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(54) Title: GROUP B STREPTOCOCCUS VACCINE

(57) **Abstract:** This application relates to improved Group B Streptococcus ("GBS") saccharide-based vaccines comprising combinations of GBS polysaccharides with polypeptide antigens, and *vice versa*, such that the polypeptide and the saccharide each contribute to the immunological response in a recipient. The combination is particularly advantageous where the saccharide and polypeptide are from different GBS serotypes. The combined antigens may be present as a simple combination where separate saccharide and polypeptide antigens are administered together, or they may be present as a conjugated combination, where the saccharide and polypeptide antigens are covalently linked to each other. Preferably, the immunogenic compositions of the invention comprise a GBS saccharide antigen and at least two GBS polypeptide antigens, wherein said GBS saccharide antigen comprises a saccharide selected from GBS serotype Ia, Ib, and III, and wherein said GBS polypeptide antigens comprise a combination of at least two polypeptide or fragments thereof selected from the antigen group consisting of GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691.

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## GROUP B STREPTOCOCCUS VACCINE

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This application claims the benefit of U.S. Provisional Patent Application Serial No. 60/410,839, filed September 13, 2002, which application is incorporated herein by reference in its entirety.

### TECHNICAL FIELD

10 This invention relates to polysaccharides from the bacteria *Streptococcus agalactiae* (GBS) and to their use in immunisation.

### BACKGROUND ART

Once thought to infect only cows, the Gram-positive bacterium *Streptococcus agalactiae* (or “group B streptococcus”, abbreviated to “GBS” (Ref. 1) is now known to cause serious disease, 15 bacteremia and meningitis, in immunocompromised individuals and in neonates. There are two types of neonatal infection. The first (early onset, usually within 5 days of birth) is manifested by bacteremia and pneumonia. It is contracted vertically as a baby passes through the birth canal. GBS colonises the vagina of about 25% of young women, and approximately 1% of infants born via a vaginal birth to colonised mothers will become infected. Mortality is between 50-70%. The second 20 is a meningitis that occurs 10 to 60 days after birth. If pregnant women are vaccinated with type III capsule so that the infants are passively immunised, the incidence of the late onset meningitis is reduced but is not entirely eliminated.

The “B” in “GBS” refers to the Lancefield classification, which is based on the antigenicity of a carbohydrate which is soluble in dilute acid and called the C carbohydrate. Lancefield identified 25 13 types of C carbohydrate, designated A to O, that could be serologically differentiated. The organisms that most commonly infect humans are found in groups A, B, D, and G. Within group B, strains can be divided into at least 9 serotypes (Ia, Ib, Ia/c, II, III, IV, V, VI, VII and VIII) based on the structure of their polysaccharide capsule. In the past, serotypes Ia, Ib, II, and III were equally prevalent in normal vaginal carriage and early onset sepsis in newborns. Type V GBS has emerged 30 as an important cause of GBS infection in the USA, however, and strains of types VI and VIII have become prevalent among Japanese women.

The genome sequence of a serotype V strain 2603 V/R has been published (Ref. 2) and various polypeptides for use as vaccine antigens have been identified (Ref. 3). The vaccines currently in clinical trials, however, are based on polysaccharide antigens. These suffer from serotype-specificity and poor immunogenicity, and so there is a need for effective vaccines against 35 *S.agalactiae* infection.

It is an object of the invention to provide further and improved GBS vaccines.

## DISCLOSURE OF THE INVENTION

The inventors have realised that saccharide-based vaccines can be improved by using them in combination with polypeptide antigens, and *vice versa*, such that the polypeptide and the saccharide each contribute to the immunological response in a recipient. The combination is particularly advantageous where the saccharide and polypeptide are from different GBS serotypes.

The combined antigens may be present as a simple combination where separate saccharide and polypeptide antigens are administered together, or they may be present as a conjugated combination, where the saccharide and polypeptide antigens are covalently linked to each other.

Thus the invention provides an immunogenic composition comprising (i) one or more GBS polypeptide antigens and (ii) one or more GBS saccharide antigens. The polypeptide and the polysaccharide may advantageously be covalently linked to each other to form a conjugate.

Between them, the combined polypeptide and saccharide antigens preferably cover two or more GBS serotypes (*e.g.* 2, 3, 4, 5, 6, 7, 8 or more serotypes). The serotypes of the polypeptide and saccharide antigens may or may not overlap. For example, the polypeptide might protect against serogroup II or V, while the saccharide protects against either serogroups Ia, Ib, or III. Preferred combinations protect against the following groups of serotypes: (1) serotypes Ia and Ib, (2) serotypes Ia and II, (3) serotypes Ia and III, (4) serotypes Ia and IV, (5) serotypes Ia and V, (6) serotypes Ia and VI, (7) serotypes Ia and VII, (8) serotypes Ia and VIII, (9) serotypes Ib and II, (10) serotypes Ib and III, (11) serotypes Ib and IV, (12) serotypes Ib and V, (13) serotypes Ib and VI, (14) serotypes Ib and VII, (15) serotypes Ib and VIII, (16) serotypes II and III, (17) serotypes II and IV, (18) serotypes II and V, (19) serotypes II and VI, (20) serotypes II and VII, (21) serotypes II and VIII, (22) serotypes III and IV, (23) serotypes III and V, (24) serotypes III and VI, (25) serotypes III and VII, (26) serotypes III and VIII, (27) serotypes IV and V, (28) serotypes IV and VI, (29) serotypes IV and VII, (30) serotypes IV and VIII, (31) serotypes V and VI, (32) serotypes V and VII, (33) serotypes V and VIII, (34) serotypes VI and VII, (35) serotypes VI and VIII, and (36) serotypes VII and VIII.

Still more preferably, the combinations protect against the following groups of serotypes: (1) serotypes Ia and II, (2) serotypes Ia and V, (3) serotypes Ib and II, (4) serotypes Ib and V, (5) serotypes III and II, and (6) serotypes III and V. Most preferably, the combinations protect against serotypes III and V.

Protection against serotypes II and V is preferably provided by polypeptide antigens. Protection against serotypes Ia, Ib and/or III may be polypeptide or saccharide antigens.

Preferably, the immunogenic composition comprises one or more serogroup V antigens or fragments thereof selected from the antigen group consisting of GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358,

GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691. Preferably, the composition comprises a composition of at least two of these GBS antigens or a fragment thereof.

In one embodiment, the immunogenic composition comprises a GBS saccharide antigen and at least two GBS polypeptide antigens or fragments thereof, wherein said GBS saccharide antigen comprises a saccharide selected from GBS serotype Ia, Ib, and III, and wherein said GBS polypeptide antigens comprise a combination of at least two polypeptide or a fragment thereof selected from the antigen group consisting of GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691.

Preferably, the combination comprises GBS 80 or a fragment thereof. In one embodiment, the GBS polypeptide antigens comprise a combination of two GBS antigens or fragments thereof selected from the antigen group consisting of (1) GBS 80 and GBS 91, (2) GBS 80 and GBS 104, (3) GBS 80 and GBS 147, (4) GBS 80 and GBS 173, (5) GBS 80 and GBS 276, (6) GBS 80 and GBS 305, (7) GBS 80 and GBS 313, (8) GBS 80 and GBS 322, (9) GBS 80 and GBS 328, (10) GBS 80 and GBS 330, (11) GBS 80 and GBS 338, (12) GBS 80 and GBS 358, (13) GBS 80 and GBS 361, (14) GBS 80 and GBS 404, (15) GBS 80 and GBS 656, (16) GBS 80 and GBS 690, and (17) GBS 80 and GBS 691.

Still more preferably, the combination is selected from the antigen group consisting of (1) GBS 80 and GBS 338; (2) GBS 80 and GBS 361, (3) GBS 80 and GBS 305, (4) GBS 80 and GBS 328, (5) GBS 80 and GBS 690, (6) GBS 80 and GBS 691 and (7) GBS 80 and GBS 147. Even more preferably, the combination comprises GBS 80 and GBS 691.

In one embodiment, the composition comprises a combination at least three GBS polypeptide antigens. Preferably, this combination comprises GBS 80 and GBS 691.

Preferably, the immunogenic composition further comprises a GBS polypeptide or a fragment thereof of serogroup II.

#### ***The polypeptide antigen***

The polypeptide is preferably: (a) a polypeptide comprising an amino acid sequence selected from the group consisting of the even-numbered SEQ IDs 2-10966 from Ref. 3; (b) a polypeptide comprising an amino acid sequence having sequence identity to an amino acid sequence from in (a); or (c) a polypeptide comprising a fragment of an amino acid sequence from (a).

Within (a), preferred SEQ IDs are those which encode GBS1 to GBS689 (see Table IV of reference 3).

Within (b), the degree of sequence identity may vary depending on the amino acid sequence (a) in question, but is preferably greater than 50% (e.g. 60%, 70%, 80%, 90%, 95%, 99% or more).

Polypeptides within (b) include homologs, orthologs, allelic variants and functional mutants of (a). Typically, 50% identity or more between two proteins is considered to be an indication of functional

equivalence. Identity between proteins is preferably determined by the Smith-Waterman homology search algorithm as implemented in the MPSRCH program (Oxford Molecular), using an affine gap search with parameters *gap open penalty*=12 and *gap extension penalty*=1.

Within (c), the length of the fragment may vary depending on the amino acid sequence (a) in question, but the fragment is preferably at least 7 consecutive amino acids from the sequences of (a) e.g. 8, 10, 12, 14, 16, 18, 20, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more. Preferably the fragment comprises one or more epitopes from the sequence. Other preferred fragments are the N-terminal signal peptides of SEQ IDs 1-10966 from Ref. 3, SEQ IDs 1-10966 from Ref. 3 without their N-terminal signal peptides, and SEQ IDs 1-10966 from Ref. 3 wherein up to 10 amino acid residues (*i.e.* 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 residues) are deleted from the N-terminus and/or the C-terminus *e.g.* the N-terminal amino acid residue may be deleted.

The polypeptides can, of course, be prepared by various means (*e.g.* recombinant expression, purification from GBS, chemical synthesis *etc.*) and in various forms (*e.g.* native, fusions, glycosylated, non-glycosylated *etc.*). They are preferably prepared in substantially pure form (*i.e.* substantially free from other streptococcal or host cell proteins) or substantially isolated form.

Preferred polypeptide antigens are: GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691, including polypeptides having amino acid sequences with sequence identity thereto *etc.*

The nucleotide and amino acid sequences of GBS80 in Ref. 3 are SEQ ID 8779 and SEQ ID 8780. These sequences are set forth below as SEQ ID NOS 1 and 2:

#### **SEQ ID NO. 1**

ATGAAATTATCGAAGAAGTTATTGTTTCGGCTGCTTTAACATGGTGGCGGGGTCAACTGTTGAACCAGTAGCTCAGTTGC  
25 GACTGGAATGAGTATTGTAAGAGCTGCAGAAGTGTACAAGAACGCCAGCGAAAACAAACAGTAAATATCTATAAATTACAAGCTG  
ATAGTTATAAATCGGAATTACTTCTAATGGTGGTATCGAGAATAAAGACGGCAAGTAATATCTAACTATGCTAAACTTGGTGAC  
AATGAAAAGGTTCAAGGCTACAGTTAACGTTATAAAGCTCAAGACGGTATTTCCTGATGAATGAAATTGAAAAATTGACAAC  
AGTTGAAGCAGCACGATGCAAAAGTTGGAACAGATTCTGGAGAAGGTGCTACCTACCTCAAACAAACTAATGCTCAAGGTTGGTGC  
TCGATGCTCTGGATTCAAAGAATGAGATACTTGTAGAGAAGATTAAAGAATTCACCTCAAACATTACCAAAGCTTAT  
GCTGTAACGGTTGTGGATTACCAAGTTGCTAACTCTACAGGTACAGGTTCTTCTGAAATTAAATTACCTAAACGTT  
30 TGTAACGTGATGAAACAAAAACAGATAAAAGATGTTAAAAATTAGGTCAAGGACGATGCAAGGTTATACGATTGGTGAAGAATTCAAAT  
GGTTCTTGAATCTACAATCCCTGCCAATTAGGTGACTATGAAAATTGAAATTACTGATAAATTGCAAGATGGCTGACTTAT  
AAATCTGTTGAAAAATCAAGATTGGTTGCAAAACACTGAATAGAGATGAGCAGTACACTATTGATGAACCAACAGTTGATAACCA  
AAATCACATTAAATTACGTTAAACACAGAGAAAATTAAAGAAAATTGCTGAGCTACTTAAAGGAATGACCTTGTAAATTCAAG  
ATGCTCTGATAAAAGCTACTGCAAATACAGATGCGCATTGGAAATTCCAGTGGCATCAACTATAATGAAAAGCAGTT  
35 TTAGGAAAAGCAATTGAAAAATTCTTGAACATTCAATATGACCCATCTCTGATAAAGCTGACAATCCAAAACCATCTAATCCTCC  
AAGAAAACCAAGCTCATACTGGCGGAAACGATTCTGAAAGAAAAGACTCAACAGAAAACACAAACACTAGGTGGTGTGAGTTG  
ATTGTTGGCTCTGATGGGACAGCAGTAAATGGACAGATGCTCTTATTAAAGCGAATACTAATAAAAACATATTGCTGGAGAA  
GCTGTTACTGGGCAACCAATCAAATTGAAATCACATACAGCGTACGTTGAGATTAAAGGTTGGCTTATGCAGTTGATGCGAA  
40 TGCAGAGGGTACAGCACTTACAAATTAAAGAAAACAAAGCACCAGAAGGTTATGTAATCCCTGATAAAGAAATCGAGTTA  
CAGTATCACAAACATCTTATAATACAAAACCAACTGACATCACGGTGTGATGCAACACCTGATAACAATTAAAACAAAC  
AAACGTCCTTCAATCCCTAATACTGGTGGTATTGGTACGGCTATTTGTCGCTATCGGTGCTGCGGTATGGCTTTGCTGTTAA  
GGGGATGAAGCGTCGTACAAAAGATAAC

#### **SEQ ID NO. 2**

45 MKLSKLLFSAAVLTMVAGSTVEPVAQFATGMSIVRAAEVSQERPAKTTVNIYKLQADSYKSEITSNGGIENKDGEVISNYAKLD  
NVKGLQGVQFKRYKVKTDISVDELKKLTTVEAADAKVGTILEEGVSLPQKTNQGLVVDALDSKSNSVRLYVEDLKNSPSNITKAY  
AVPFVLELPVANSTGTGFLSEININYPKNVTDEPKTDKDVKKLGQDDAGYTIGEEFKWFLKSTIPANLGDYEFKEITDKFADGLTY  
KSVGKIKIGSKTLNRDEHYTIDEPTVDNQNTLKTFPEKFKEIAELLKGMLTVKNQDALDKATANTDDAAFLEIPVASTINEKAV

LGKAIENTFELQYDHTPDKADNPKPSNPPRKPEVHTGGKRFVKKDSTETQTLGGAEFDLLASDGTAVKWTDALIKANTKNYIAGE  
AVTGQPIKLKSHTDGTFEIKGLAYAVDANAEGTAVTYKLKETKAPEGYVIPDKEIEFTVSQTSYNTKPTDITVDSADATPDTIKNN  
KRPSIPNTGGIGTAIFVAIGAAMAFAVKGMRRTKDN

5 The nucleotide and amino acid sequences of GBS 91 in Ref. 3 are SEQ ID 8937 and SEQ ID

8938. These sequences are set forth below as SEQ ID NOS 3 and 4:

#### SEQ ID NO. 3

10 ATGAAAAAAAGGACAAGTAAATGATACTAAGCAATCTTACTCTCTACGTAATATAAATTGGTTAGCATCAGTAATTTAGGGTC  
ATTCTATAATGGTCACAAGTCCCTGTTTGCAGATCAAACACTACCGTTCAAGTAATAATCAGACAGGACTAGTGTGGATGCTA  
ATAATTCTCCAATGAGACAAGTGCCTAAGTGTGATTACTTCAATAATGATAGTGTCAAGCGCTCTGATAAAAGTTGAAATAGT  
CAAATACGGCAAAGAACAGGACATTACTACTCTTTAGTAGAGACAAGCCAATGGTGGAAAAAACATTACTGAACAAGGGAAATT  
TGTGTTAGTAGCAAAAGAACAGGAGGTGAAAAAACACCTTCAAAATCAGGCCAGTAGCTTCTATGCAAAGAACAGGATGAAAGTT  
TCTATGACCAAGTATTAATAAAGATAATGTGATTGTTACATAAGTCTTTGGCGTAGCTGATAACGAGCTATTGAG  
TCACTAGATCCATCAGGAGGTTCAAGAGACTAACGACCTACTCCTGTAACAAATCAGGAAGCAATAATCAAGAGAAAATAGCAAC  
15 GCAAGGAAATTATACATTTCACATAAAAGTAGAAGTAAAGGTAAGGCTAAGGTAGCGAGTCCAACCTCAATTACATTGGACAAAG  
GAGACAGAATTGTTACGACCAAATACTAATATTGAAGGAAATCAGTGGTATCTTATAAAATCATTCAATGGTGTGCTGTTT  
GTTTTGCTAGGTAAAGCATCTCAGTAGAGAAAAACTGAAGATAAAGAAAAAGTGTCTCCTCAACCACAAGGCCGTATTACTAAAAC  
TGGTAGACTGACTATTTCTAACGAAACAACTACAGGTTTGATATTAAATACGAATATTAAGATGATAACGGTATCGTGTGCTG  
TTAAGGTTACCGGTTGGACTGAAACAAGGAGGGCAAGATGATATAAATGGTATACAGCTGTAACTACTGGGATGGCAACTACAAA  
20 GTAGCTGTATCATTGCTGACCATATAAGAATGAGAGGCTTTTATAATATTCAATTACGACAGGCTTAACTACGAGCTGTT  
AGGTGTAACAGGAACCTAAAGTGACAGTAGCTGGAACACTATTCTCTCAAGAACCTATTGAAAATGGTTAGCAAAGACTGGTGT  
ATAATATTATCGGAAGTACTGAAGTAAAAATGAAGCTAAATATCAAGTCAGACCCAATTACTTTAGAAAAAGGTGACAAAATA  
AATTATGATCAAGTATTGACAGCAGATGGTACCTAGTGGTTCTACAAATCTTATAGTGGTGTGCTGCTATATTCTGTGAA  
AAAGCTAATACAAGTAGTGAAAAAGCGAAAGATGAGGGCAACTAACCGACTAGTTATCCAACTTACCTAAAACAGGTACCTATA  
25 CATTCAACTAAACGTTAGATGTGAAAAGTCACACCTAAAGTATCAAGTCCAGTGGAAATTAAATTTCAAAAGGTGAAAAAAACAT  
TATGATCAAGTGTAGTAGATGGTCATCAGTGGATTTCATACAAGAGTTATTCCGGTATTGCTGCTATATTGAAATT

#### SEQ ID NO. 4

30 MKKGQVNDTKQSYSLRKYKFLASVILGSFIMVTSVFAQDTTSVQVMNQGTGTSVDANNSSNETSASSVITSNNDSVQASDKVVNS  
ONTATKDITPLVETKPMVEKTLPEQGNVYYSKETEVKNTPSKSAEVAFYAKKGDKVFYDQVFNKDNVKWISYKSFGRVRRYAAIE  
SLDPSSGSETKAPTPVTNSGSNNQEKIAQTQGNYTFSHKVEVKNEAKVASPTQFTLKDGRIFYDQILTIEGNQWLSSYKSFNGVRRF  
VLLGKASSVKEKTDKEVSPQPQARITKTGRLTISNETTTGFDILITNIKDDNGIAAVKPVWTEQGGQDIKWKYTAVITGDGNYK  
VAVSFADHKNEKGLYNIHLYQEASGTLVGVGTGKTVAGTNSSQEPFENGLAKTGVYNIIGSTEVKNEAKISSQFTLEKGDKI  
NYDQVLITADGYQWISYKSYSVGRYYIPVKKLTTSEKAKDEATKPTSPNLPKTGTFTKTVDVKSQPKVSSPVEFNFKGEKI  
35 YDQVLVVDGHQWIISYKSYSGIRRYIEI

The nucleotide and amino acid sequences of GBS 104 in Ref. 3 are SEQ ID 8777 and SEQ

ID 8778. These sequences are set forth below as SEQ ID NOS 5 and 6:

#### SEQ ID NO. 5

40 ATGAAAAAGAGACAAAAAAATGGAGAGGGTTATCAGTTACTTACTAATCTGCCCCAAATTCCATTGGTATATTGGTACAAGG  
TGAAACCCAAGATACCAATCAAGCATTGAAAAGTAATTGTTAAAAAAACGGGAGACATGCTACACCTTACGGCAAAGCAGCTT  
TTGTGTTAAAAAAATGACAATGATAAGTCAGAAAAGTCAGCAAACGGTAGAGGGTTCTGGAGAAGCAACCTTGGAAAAGTTGAGATAA  
CCTGGAGACTACACATTAAAGAGAAGAACAGCACCAATTGGTTATAAAACACTGATAAAACCTGGAAAGTTGAGATAA  
CGGAGCAACAATAATCGAGGGTATGGATGAGATAAAAGCAGAGAACAGAAAAGTGTGAGATGCCAATATCCAAATCAGCTA  
45 TTTATGAGGATACAAAGAAAATTACCCATTAGTTAAATGAGAGGGTTCCAAAGTTGGTGAACAATACAACAGCATTGAATCCAATA  
AATGGAAAAGATGGTCAGAGAGAGATGGTGAAGGGTTGTTATCAAAAAAATTACAGGGTCAATGATCTCGATAAGAATAAATA  
TAAAATGAAATTAACTGGTGGGTTAAACCACTGGTGAACAGGAAACTTAACCAACTAGATGTTGCTTATAGTGGTGTGCTATTAGATA  
ATTCAAATAGTATAAATGAAAGAGCCAATAATTCTCAAAGAGCATTAAAGCTGGGAGAGCAGTTGAAAGCTGATTGATAAA  
ATTACATCAAATAAAGACAATAGAGTAGCTTGTGACATATGCCAACCATTTGATGGTACTGAAGCGACCGTATCAAAGGG  
50 AGTTGCCGATCAAAATGGTAAAGCGTGAATGATAGTGTATCATGGGATTATCATAAAACTACTTTACAGCAACTACACATAATT  
ACAGTTATTTAAATTAAACAATGATGCTAACGAAGTTAATATTCTAAAGTCAGAAATTCCAAAGGAAGCGGAGCATATAATGGG  
GATCGCACGCTCTATCAAATTGGTGCAGACATTACTCAAAAGCTCTAATGAAAGCAAAATGAAATTAGAGACACAAAGTTCTAA  
TGCTAGAAAAAAACTTATTTCACGTAACGATGGTGTCCCACGGATGTTATGCCATAAAATTCTTATATCAAACAT  
CTTACCAAAACGTTAAATTCTTTTAAATAAAACAGATAGAAGAGGGTATCTCCAAGGAGTTTATAATCAATGGTGT  
55 GATTCAAATAGTAAAGGAGATGGAGAGAGTTAAACTGTTGGTGTGAGATGGGATATGCAATTAAATGTTGATGATATTCTCTATGG  
AGCTTATGAGTACCGCAAATCAACTCTCTGTAATGAGTAATGAGGATATGCAATTAAATGTTGATGATATTCTCTATGG  
GAGATTACAACGGGCTATCCATTGATCCTAACGACAAAGAACAGGAAACTCTGCAACGAAACAAATCAAACACTCATGGTGTGAGCAAC  
ACATTATACTTTAATGGAAATATAAGACCTAAAGGTTATGACATTGTTACTGTTGGGATTGGTGTAAACGGAGTCTGGTGCAC  
TCCTCTGAGCTGAGAAATTATGCAATCAATCAAGTAAACAGAAAATTACTAATGTTGATGATGACAAATAAAATTATG  
60 ATGAGCTAAATAACTTTAAACAAATTGTTGAGGAAAACATTCTATTGTTGATGGAAATGTTGACTGATCCTATGGGAGAGATG  
ATTGAAATTCCAATTTAAAGGGTCAAAGTTTACACATGATGATTACGTTTGGGAAATGATGGCAGTCAGTCAATTAAAAATGG  
TGTGGCTTGGTGGACCAAACAGTGTATGGGGAAATTAAAAGATGTTACAGTGTACTATGATAAGACATCTCAAACCATCAAA

TCAATCATTTGAACTTAGGAAGTGGACAAAAAGTAGTTCTTACCTATGATGTACGTTAAAAGATAACTATATAAGTAACAAATT  
 TACAATACAAATAATCGTACAACGCTAAGTCGAAGAGTGAAAAAGAACCAAATACTATTCGTGATTTCCAATTCCAAAATT  
 5 TGATTTCTCGTGGAGCTACTAACCATCAGTAATCAGAAGAAAATGGGTGAGGTTGAATTATTAAAGTTAATAAAGCACAAAC  
 ATTCAAGAACATCGCTTGGGAGCTAAGTTCACTTCAGATAGAAAAGATTTCTGGGTATAAGCAATTGTTCCAGAGGGAAAGT  
 GATGTTACAACAAAGAACATGATGGTAAAATTATTAAAGCACTTCAGATGGTAACTATAAATTATGAAATTTCAGTCAGCCAGA  
 TGGCTATATAGAGGTTAAAACGAAACCTGGTGACATTACAATTCAAATGGAGAGTTACGAACCTGAAAGCAGATCCAAATG  
 CTAATAAAATCAAATCGGTATCTGAAGGAAATGGTAAACATCTTATTACCAACACTCCAAACGCCACCAGGTGTTTCT  
 AAAACAGGGGAATTGGTACAATTGTCATAATTAGTTGGTCTACTTTATGATACTTACCATTTGTTCTTCGCTCAAACA  
 ATTG

10

**SEQ ID NO. 6**

MKKRQKIWRGLSVLLILSQIPFGILVQGETQDTNQALGVIVKKTGDNATPLGKATFVLKNDNDKSETSHETVEGSGEATFENIK  
 PGDYLTREETAPIOGYKKTDKTVKVKVADNGATIIEGMDADKAEKRKVEVLNAQYPKSAYEDTKENYPLVNVEGSKVGEQYKALNPI  
 NGKDGRREIAEGWLSKKITGVNDLKDKNKYKIELTVEGKTTVETKELNQPLDVVLLDNNSMNNEARRANSQRALKAGEAVEKLIDK  
 15 ITSNDNRVNLAVTYASTFDGTEATPSKGVDQNGKALNPSWDYHKTFTATTHNSYSLNLTNDANEVNILKSRIPEKEAHING  
 DRTLYQFQGATFTQKALMKANEILETQSSNARKKLIFHVTDGVPTMSYAINFPNPYISTSQNFNSFLNKLPDRSGILQEDFTIINGD  
 DYQIVKGDGESFKLFSDRKPVPTGGTTQAAAYRVPQNQLSVMNSNEYAINSGYIYLYWRDYNWVYPFDPKTKKVSAWKQIKTHGEPT  
 TLYFNGNIRPKGYDIFTVGIVGNPDGPATPLEAEKFMQSISSKTENEYTNVDDTNKIYDELNKYFKTIVEEKFHSIVDGNVTDPGMEM  
 IEFQLKNGQSFTHDDYLVGNQSQLKNGVALGGPNSDGGILKDVTVTYDKTSQTICKINHLNLGSGQKVVLTYDVRLKDNYISNKF  
 20 YNTNNRTTLSPSKSEKEPNTIRDFPIPCKRDVREFPVLTISNQKMGVEFVIKVNKDKHSESILLGAKFQLQIEKDFSGYKQFVPEGS  
 KTTPKNDGKJYFKALQDGNYKLYEISSPDGYIEVKTKPVTFTIQNGETVNLKADPNANKNQIGYLEGNNGKHLITNTPKRPPGVFP  
 KTGGIGTIVYILVGSTFMILTCFSRRKQL

The nucleotide and amino acid sequences of GBS 147 in Ref. 3 are SEQ ID 8525 and SEQ  
 25 ID 8526. These sequences are set forth below as SEQ ID NOS 7 and 8:

**SEQ ID NO. 7**

GTTGGATAAAACATCACTCAAAAAGGCTATTTAAAGTTAACACTAGTATTATTAATGCATAGCAATCAAGTGAATGCAGAGGAG  
 CAAGAAACAAAACCAAGAGCAATCACCTGTAATTGCTAAGTGTCAACAGCCATCGGTAACTACTAATACTGTTGAAAAAAACATCT  
 30 GTAAACAGCTGCTCTGCTAGTAATACAGGGAAAAGATGGTGTATCATCTGTAACATCTGTAACAAATGACAAAAGAGATGAATTATTAGAAAGAGTTATCT  
 AAAACACTGTATGCTTAATGGGGCTGATCTGAAGAGAAAATCCCCTCAAGGAGGTGAAGCCAGAAAGCAAGTCATCGCTGCTGTTGATACATCTAAA  
 AATGCTCAACTGCAATAGCACAGAAAGTCTCCCTCAGCATATGAAGAGGTGAAGCCAGAAAGCAAGTCATCGCTGCTGTTGATACATCTAAA  
 ATAACAAAATTAACAGCCATAACCCAAAGAGGAAAGGGAAATGTAAGTGTACTATTGATACTGGCTTGTGATATTAAACCATGATATTCTCGTTTA  
 GATAGCCCCAAAGAGTGTAAAGCAGCTTTAAACAAAGCAGAAATTTGAGGAATTAAAGCAGAAACATAATTAACCTTACTATTGGGAAATGGGTTAAC  
 GATAAGATTGTTTGCACATAACTACGCCAACATAAGAACAGTGGCTGATAATTGCAAGCAGTATGAAAGATGGTTATGGTCAAGAACAGAAG  
 35 AATATTTCGCATGGTACACAGTGTGTGTTTTGTAGGTAATAGTAAACGTCAGCAATCAATGGCTCTTTAGAGGTGAGCGCCAAAT  
 GCTCAAGTCTTAAATATGCGTATTCAGATAAAATTGATTGCGACAAATTGGTGTGAAAGCATATGCTAAAGCAATCACAGACGCTGTTAATCTAGGA  
 GCACAAACGATTAATATGAGTATTGGAAACACGCTGTTTAAATGCTCTGATATAAGTAAAGTAAATTAGCCTAATGGTCAAG  
 GGCCTTGCAGTTGGTGGCTGCCGAAATTTGGTGTGTTATGCAACACATTATCAACTATCTGACTACGGTACCGTTAAT  
 AGTCCAGCTAITCTGAAGATACTTGAGTGTGTGACTATGAATCACTTAAACTATCACTGAGGTGTTGAAACAACTATTGAAGGTAAGTTA  
 40 GTTAAAGTTGCCATTGTGACTCTAAACAGGTTAACAGTGTGTTATGCAACAGGCTTACGGATGTGGTTATGCCAAATTATGTCGAAAAAGACTTGAAGGT  
 AAGGACTTTAAAGGTAAGATTGCAATTGAGCGTGGTGGGACTGTGTTATGACTAACTCATGCTACAAATGCAAGGTGTTGGT  
 ATCGCTTATTGTTAACAGTCAAGAAAACGTTGAAATTCTTAACCTTACCGTGAATTACCTGTTGGGATTATTAGTAAAGTAGATGGCAGGCGT  
 ATAAAAAAACTTCAAGTCAGTTAACATTAAACAGAGTTTGAGTGTAGTTGAGTGTAGGCAAGGTGGTAATGTTGCAACATCACTGGGGC  
 GTGACAGCTGAAGGAGCAATCAAGGCTGATGTAACAGCTCTGGCTTGTGAAATTATTCTCAACCTATAAATCAATACAAAACAATGCTGGT  
 45 ACAAGTATGGCTCACACATGTCAGGATTAAATGCAACATGCTTCAAGGCTTACGGATGTGGTTATGCCAAATTATGTCGAAAAAGACTTGAAGGT  
 TTGCTAGAATTGCTTAAACACATCCTCATGAGCTCAGAACAGCATTATGAGTGAAGGAGGATAAGGGCTTTATTACACAGTCAGCAAGGTGCA  
 GGTGTAGTTGATGCTAAAAAGCTATCCAAGCTCAATTATGAGTGAAGGAGGATAAGGGCTTAAACAGCAATGGAGATAAAA  
 50 TTTGATATCACAGTTACAATTCTAAACAGTGTAGAAGGTGTCAAAGAATTGTTATTCAAGCTAATGTAAGCAACAGAACAGTAATAAAGGTTAAA  
 TTGCTTAAACACAGCCTGCTGAGTACTAACTGGCAGAAAGTCAATTCTCTGCTGATAACAGAACAGTCAATTGAGTGTAGTGTAGTGTAGT  
 CAATTAGTCAAGAAATTAAAAGAACAGTCAGGAAATGTTATTCTTCAAGGTTGTTGAGTGAAGGTTTAAAGAACAGCAAGGAGTACTATTGAGTGTAGT  
 ATGAGTATTCTTTGAGGATTTAATGCTGATTGCTGAAACTACAAGCAGCTTAAACCCGATTATAAGACGCTTCTAAAGGTAATTCTAC  
 55 TATAAAACCAAAATGATACAACCTATAAAGCCAATTGGAGTACAATGAATCAGCTCTTTGAAAGCAACAACTATACTGCTCTGTTAACAAATCA  
 GCCCTCTGGGCTATTGTTGATATTGCTAAACGGGGAGGTTAGAATTGCAACCGGAGACTCAAAAGAATTATTAGGAACTTTGAGAAT  
 AAGGTTGAGGATAAAACATTCTATTGAAAGAGATGCAAGGCAATAACCATATTGCTTCAAGGTTCTCCAAATAAAGGAAATGGGAAATGGGACGAA  
 60 ATCACTCCCCAGCAACTTCTTAAGAAATGTTAAGGATATTCTCTGCTCAAGGTTCTAGATCAAAATGAAATTGTTATTGCTTCAAGGTT  
 CCATCTTATCGTAAAAATTCCATAATAACCAAGCAAAGTGTGGTCATTATGCTATGATGCTCTTCAGTGGAGTGGTTAGATAAGGATGGC  
 AAAGTTGAGCAGGGTTTATCTTACCTACGCTTACACACCAGTCAAGGAGCAGAACATAGTCAGGAGTCAGACTTAAAGTACAAGTA  
 AGTACTAAGTCACCAAACTCTCTCAGAGCTCAGTTGAGTAAAGCTAATGCAACATTAAGCTTACGCTTACGCTTACGCTTAC  
 ACATATCGTTTACAATTAGTTTATCTCATGTTGAAAGATGAAAGATATGGGAGTGGAGACTTCTTACCATATTCTTACATATGCAAGAACAGT  
 65 AAAGTGAACACTCCTAAACGGTTAACGATAGGGAGAGTGAGGTTGGCTAGACCTAAGGCCCTGACACTTGTGTGAGAATAAGCTGGTAAT  
 TTGCGAACGGTAAATTGCTGATCTTGTGAAATAAGGAGTGTGTTAAAGGAGGAAAGAACGCTATGTAATTCTAACAGCTTCAAATTATTGAT  
 AACCTGAAAAAGAACCTATGTTATTCTAAAGAAAAGAGAAAAGAGTAAACAAAGAATCTAGAAGGAAATAATTAGTTAAGCCGCAAACACTAC  
 ACTACTCAATATTGCTAAAGAAATACTAAACATCAGGAAATGAGGAAAGTCTCACTTCAACAAACATAATTAGTAGCAGAGTAGCTAAGATCATA  
 TCACCTAAACATAACGGGGATTGTTAACCATACCTTACTAGTACATCAGATAGAGCAACGAATGGTCTATTGTTGACTTGGCATTGTT  
 TCTAGTTACTCTTATTGAAACCCAAAAGACTAAAATAATGTTAA

**SEQ ID NO. 8**

VDKHHSKKAILKLTLLITTSILLMHSNOVNAEEQELKNQEQQSPVIANVAQQPSPSVTNTVEKTSVTAASASNTAKEMGDTSVKNDKTEDELLEELS  
 KNLDTSNLGADLEEYPSKPETTNKESNVVTNASTAIAQKVPSSYEVKPEKSSLAVLDTSKITKLQAITQRGKGNVVAIIDTGFIDNHDI FRL

5 DSPKDDKHFSFKTKEFEELAKAHNITYGKWVNDKIYFAHNYYANNTETVADIAAAAMKDGYGSEAKNISHGHTHAGIIVGNSKRPAINGLLEGAAPN  
AQVLLMIRIPDKIDSDFGEAYAKAITDAVNLSGAKTINMSIGKTADSLIALNDVKLALKLASEKGVAVVVAAGNEGAFGMDYSKPLSTPDYGTVN  
SPAISEDTLSVASYESLKIISSEVVEETIEGKLVLKLPIVTSKPKFDKGAYDVVYANYGAKKDFEGKDFKGKIALIERGGGLDFMTKITHATNAGVVG  
IVIFNDQEKRGNFLIPYRELPGIISKVDGERIKNTSSQLTFNQSFEVVDQSQGGNRMLEQSSWGVTAEGAIPKDVTAASGEIYSSSTNNQYQTMSG  
10 TSMASPHVAGLMTMLQSHSLAEKYKGMLDSKKLLELSKNILMSSATALLYSEEDKAFYSPRQQGAGVVDABEKAIIQAQYITTGNDGAKAINLKRMDK  
FDITVTIHKLVEGVKELYQQANVATEQVNKGKFKALPKPQALLDTNWQKVILRDKETQVRFTIDASQFSQKLKEQMANGYFLEGFVRFKEAKDSNQEL  
MSIPFGVNGDFANLQALETPYKTLSKGSFYYKPNDDTHKDQLEYNESAPFESNNYTALLTQSASWGVVVDYVKNNGEELAPESPRIILGTFEN  
KVEDKTIHLRLERDAANNPFAISPNDGRDEITPQATFLRNVDISAQVLDQNGNVIWQSKVLPSSYRKFNHFNNPKQSDGHYRMDALQWSGLDKD  
KVADGFYTYRLRYTPVAEGANSQESDFKVVQVSTKSPNLPSSRAQFDETNRTLSLAMPKESSYVPTYRLQLVLSHVVKDEYGDETSYHYFHDOEG  
KVTLPKTVKIGESEVAVDPKALTIVVEDKAGNFATVQLSDDLNAKVVSEKENAIVISNSFKYFDNLKKEPMFISKKEVWNKNULEELILVVKPQTIV  
TTQSLSKIEITKSGNEKVLSTNNNSRVAKIISPXHNGDSVNHLPSTSADRNGLFVGTLLALLSSLLLKPKKTKNNSK

The nucleotide and amino acid sequences of GBS 173 in Ref. 3 are SEQ ID 8787 and SEQ ID 8788. These sequences are set forth below as SEQ ID NOS 9 and 10:

#### 15 SEQ ID NO. 9

ATGAAACGTAATACTTTATTCTTAATACGGTGACGGTTAACGTTAGCTGCTGCAATGAATACTAGCAGTATCTATGCTAATAGTACTGAGACA  
AGTGCCTACTAGTCTCTACTACAAATACTATCGTCAAACAACTATGACAGTAATCTCCAAAATTTGCTATCAGAACTCAGGACAATCTGTAATA  
GGTCAGTAAACCAAGATAATTGKQFALKPQALLDTNWQKVILRDKETQVRFTIDASQFSQKLKEQMANGYFLEGFVRFKEAKDSNQEL  
10 CCTGCTGTTGAGAGTACTCTACTAAGTTAACGAGAGACTTACAAACAAAAGATGGTCAGAAGTTTACGCCAACATGCTGAGAAGTGTGCAAGTT  
ACTAGTGAGGAACCTGTTAATATGCCATACGATATTATGCTAAAGAAAACCCATCTTAAATGCTAGTCACTACTAGACGCCAACAGCTATT  
GAAGAGGCTGAAAAACCTTAAAGATAACCATCAGCCGTTTTAGGTGTTCCCTGTTAGTCAGGTTAGGGCTACAGTATTAAAGGTGCTGAAACC  
AATAATGGCTGATCTATGAGATGAAAGGAAATTTAGCAGATTTAGCTGAGCTATGCTATGCTAAAGATTTAGGATTATATTAGGATTA  
ACGAACCTTCCAGAGTATGGTGGCGTAATATAACAGATCTAAATTACCGCTCTAACGCCATAATCCTTGGATCTTCTCATAATGCTGGTGGC  
20 TCTTCTGGTGGAAAGTGCAGCAGCCATTGCTAGCGGAATGACGCCAATTGCTAGCGGTAGTGTAGCTGGTGGTTCTATCCGATTCCATCTCTGG  
ACGGGCTTGGTAGGTAAAACCAACAAAGAGGATTGGTAGTAATGAAAGGAGCAGATTGCTATAGTCAGCAGTTCAATTCCATTAACTAAGTC  
TCTAGAGACGCCAGAACACATTATACTTACGTTACAGCTGATTATCAAAACGCTTATGACACGTTACGCTTACCCAGCTACAGTATCCGACTTAC  
30 TTGAAATCACCAGGAAACATTGATGGTAGACGATTAACTGGCTGATTATCAACCTGGCTATTGGCATGGGAGGCTTTCAACAATTGAAAAGAC  
TTAAAAAAACATGGTTTACTAAAGAAGACGTTGATCCTATTACTTGGGAGCTTCTGTTATCAGATAAGGCTGAACCTTAAAG  
GAGATAGACTTACCAATTGATGGTAGACGATTAACTGGCTGATTATCAACCTGGCTATTGGCATGGGAGGCTTTCAACAATTGAAAAGAC  
TTAAAAAAACATGGTTTACTAAAGAAGACGTTGATCCTATTACTTGGGAGCTTCTGTTATCAGATAAGGCTGAACCTTAAAG  
35 TCTATTATGGAAAGCCAAAACATGGTATTATGCTGAAGGCAATTGGAGGCTCACAAGCAATTCTCTTATCGCCAACGCCAGGCA  
AGTTAGGCCCTTAATACAGATCATGTAACAGAGGAAATAAAAGAGCATTATAATGAAAGGAGCAGTACTGGCTTAACAGCCTACTCCCTCTTAAAGGCT  
CTCTTAAATGCCAGTGGGAGCCTATGTCGCTAGAACACCTTTACACAAATTGCTAATATGACAGGACTCCCAGCTACAGTATCCGACTTAC  
TTATCTGAGTCGGTTTACCCATAGGGACGATGTTAATGGCAGGTCAAACACTATGATATGTTAAATTAAATTGCAACTTCTTAAAGGAC  
CATGGTTTAAATGTTAAATGCAAGAATAATGATAAGGAGTGAACCTACTGGCTTAACAGCCTACTCCCTCTTAAAGGCT  
40 TCATCATTAGTAAATTAGAAGAAAATTCAACAGGTTACTCAAGTATCTATCTTAAACAGGATGTTAAATGCTGTTAAATTAAACCTCCAGTCTGTTAGCTTAA  
ATGGCATATCAAAGAACAGGTGATAACAGAATCAAGCCTATCCAGTAACTTCTGTTAAATTAGCTGTTAGTAAACCTCCAGTCTGTTAGCTTAA  
GTAACAAAAAGAATCAGAAAAGT

#### SEQ ID NO. 10

40 MKRKYFILNTVTVLTLAAAMNTSSIYANSTETSAVASVPTTNTIVQTNDSNPTAKFVSESGOSVIGQVKPDNSAALTTVDTPHHISAPDALKTTQSS  
PVVESTSTKLTEETYKQKDGQDLANMVRSGQVTSEELVN MAYDIIIAKENPSLNAVITTRRQEAIIEARKLKDTNQPFLGVPLLVKGHLHSIKGGET  
NNGLIYADGK1STFDSSYVKYKDLGF1ILGQTNFVEGFWRNITDSKLYKLGHPWDLAHNAGGSSSGSAAAIASGMPPIASGSDAGGSIRIPSSW  
TGLVGLKPTRGLVSNEKPDSYATAVHFPPLTKSDQTLVSKLSP1IAYTLKSPMGTEVSQDAKNAIMDNVTFLRKQFGKVT  
45 EIDLPIDPGRALMRDYSTLAIGMGGAFSTIEKDLKKHCPKTDVDPITWAVHVIYQNSDKEALKKSIMEAQKHMDDYRKAMEKLHKQFPIFLSPPTA  
SLAPLNTPVTEEDKRAIYNMENLSQEERIALFNRQWEPMRLRTPFTQIANMTGLPAISIPTYLSESGLPIGTMMLMAGANYDMVLIKFATFFEKH  
HGFNVWKQRIIDKEVKPSTGLIQPTNSLFAHSSLVLEENSQVTQVSISKKWMKSSVKNPVSVMAYQKALPKTGDTESSLSPVLTLLACFSF  
VTKKNQKS

The nucleotide and amino acid sequences of GBS 276 in Ref. 3 are SEQ ID 8941 and SEQ ID 8942. These sequences are set forth below as SEQ ID NOS 11 and 12:

#### 50 SEQ ID NO. 11

50 TTGCGTAAAAAAACAAAAACTACCATTTGATAAAACTTGCCTATTGCGCTTATATCTACGAGCATCTGCTCAATGCACAATCAGACATTAAGCAAAT  
ACTGTGACAGAAGACACTCTGCTACCGAACAGCCGTTAGAACCCCCAACAACTATGAGCTTCTGAGGAACTACGATCATCAAAGGAAACTAAA  
ACCTCACAAACCTCTTCTAGTGTAGGAGAACAGCTAGCCAGATGACGCTTATGCTAGCCCTCAAGCTCTGCTAAACACTGCTGATACACCAGCA  
55 ACCTCAGGAAAGGACTATTAGGGATTGTAAGCAGCCCTCTCATGTAAGCGTGGCGCTTAACAGACAAAACGACCTTACCAATCAAAGAAAATCTGAAAAGCTAAA  
ATTGATGCTGGTTTGTAAACCATGTAAGCGTGGCGCTTAACAGACAAAACGACCTTACCAATCAAAGAAAATCTGAAAAGCTAAA  
AAAGAGCACGGTATTACCTATGGCGAGTGGGTCAATGATAAGGTTGCTTAATTACCCAGCTATAGTAAAGATGTTAAACGCTGTTGATCAAGAA  
CACGGCACACACACGGTCAAGGATCTTGTCAAGGAAATGCTCCATCTGAAATGAGGAAACCTTACCCGCTAGAAGGGTGCATGCCCTGAGGCTCAATTG  
CTTTGATGCGTGTGCAAATTGAGTACAGCTAGCAGACACTATGCTCTTACACTGCTCAAGCTATCAGAGATGCTGTCAACTTGGGAGCTAAGGTG  
60 ATTAATATGAGCTTGGTAATGCTGCACTAGCTACGCCAACCTTCCAGACGAAACAAAAAGCCTTGACTATGCCAATCAAAAGGTGTTAGC  
ATTGTGACCTCAGCTGGTAATGATAGTAGCTTGGGGCAAGGCCCTCTACCTCTAGCAGATCATCTGTTATGGGTGTTGGGACACCTGCA  
GCCGCAGATTCAACATGAGCTGGCTTACAGGCCAGAAACAGCTACTGAAAGCTACGGTCAAACACAGACGATCATCAAGATAAAAGAA  
ATGCTGTTATTCAACAAACGGTTTGGAGCCTAACAGGCTTACGACTATGCTTATGCTAATCTGTTAGGATGTTAAAGGATGTC  
GAAGGTAAAGATTGCCCTTATTGACGCTGGCGTATTGATTTCAACAGTAAAGATTGCAAAAGCTTAAAGCTGGTGTGTTAGGGGCTTGTATCTAT  
65 GACAATCAAGACAAGGGCTTCCGATTGAATTGCCAATGTTGACAGATGCCCTGCGGCCCTTATCAGTCGAAGAGACGGCTCTTTAAGCTGAAAGCAGTC  
AATCCCCCAAAACCTTACCTCAATGCGACACCTTAAGGTATTGCCAACAGCAAGTGGCACCAAACACTAAGCCGCTTCTCAAGCTGGGTCTGACA  
GCTGACGGCAATTAAACCGGATATTGACGCCCCAGAATATTGTCATCAGTGGCTAACACAAGTATGCCAAACTTCTGGAAACTAGT  
ATGCTGTCACCATTTGGTAGCGGGTATCTGGACTGTGCAAAGAATATGACACAGTATCTGATATGCAACACCATCAGAGCTTGTGTTAGCT  
GCTAAGAAAAGTATTGATGAGCTAGCAACTGCCCTATATGATGAAGATGAAAGCTTATTCTCCTCGCCAACAGGGAGCAGCAGTCGAT

5 GCTAAAAAGCTTCAGCAGCAACGATGTATGTAACAGATAAAGGACAATACCTCAAGCAAGGTTCACCTGAACAATGTTCTGATAAATTGAAAGTA  
ACAGTAACAGTTCACAAACAAATCTGATAAACCTCAAGAGTTGATTAACCAAGTAACCTGTTCAAACAGATAAAGTAGATGGAAAACACTTGCCTTG  
GCTCCTAAAGCATTGATGAGACATCATGGAAAAAAATCAAATCCAGCCAATAGCAGCAAACAAGTCACCGTCCAAATCGATGCTAGTCGATT  
AGCAAGGACTGCTTGCCCCAATGAAAATGGCTATTTCTTAGAAGGTTTGTGCTTCAAACAGATCCTAAAGAAGAGCTTATGAGCATT  
10 CCATATATTGGITTCGGAGGTGATTTGGCAATCTGTCAGCCTTGAAGAAAACCAATCTATGATGCAAAGACGGTAGCAGCTACTATCATGAAGCA  
AATAGTGTGCAAAGACCAATTAGATGGTATGGGATTACAGTTACGCTCTGAAAAATAACTTACAGCAGTACACAGAGCTAACCCATGG  
ACGATTATAACGCTGCAAAGAGGGTTGAAAACATAGAGGATATCGAACATCTCAGAGATCACAGAAACCATTTGCGAGTACTTTGCAAGG  
15 CAAGAGCCAGTGAATGCCACTACTATATCCACCGTACGCTAATGGCAAACCATATGCTGCGATCTCCAAATGGGACGGTAACAGAGATTATGTC  
CAATTGCAAGGACTCTTGCGTAAATGCTAAAACCTTGTGCTGAGCTGGGACAAAAGAAGGAAATGTTGGGACGGTAACGTGAGGAACTGG  
20 CAAGTTGTTAAACACAAATGACTTGCAGCACACTTGGTTCAACCCGTTTGGGACGGTAAAGATAAAACCGTTGGGACGGTAAAGATAAAAGACGG  
GTTGTTGCTAACCGAACCTACCTATCGTCTCGTACACGGCGATTAGCTCAGGTGCAAAGAACACACACTGATTTGATGTTGAGAC  
AATACGACACCTGAAAGTCGCAACATCGGCAACATTCTCAACAGAAGATAGTCGTTGACACTTGCACTAAACCAAAACCAGCAACCGGTTAC  
CGTGAAGCTATTGCTTACACTTATGATGAGGATCTGCCAACACAGAGTATATCTCCAAATGAGATGTTGACCTTACTCTTCTGAAGG  
25 GCTGAAGAACATGGAGGGCCTACTGTTCCATTGAAATGTCAGACTTACTATGTTGAGGATATGGCTGTTAACATCAACCTTACACAGCTG  
ACTAACCTATTGGAGGGCCTACTAATAACGGCAAACAGGGTCAAGTCAAGCAGAACAGCTAAACCCAGAACAGCGGT  
TCAGGTCAAACACCAAGATAAAAAAGAACTAAACCAAGAAAAGATAGTCAGGTAAACACCAGGTAACACTCCTAAAGGTCATCTTCT  
CGTACTCTAGAGAACGATCTTCTAAGCGTCITTAGTCACAAAAGCATCAACAGAGATCAGTTACCAACGACTAATGACAAGGATAACATCGT  
TTACATCTCTTAAGTTAGTTATGACCACCTTCTTGGG

## SEQ ID NO. 12

MRKKQKLPFDKLIALISTSIILNAQSIDI KANTVTEDTPATEQAVEPPQPIAVSEESRSSKETKTSQTPSDVGETVADDANDLAPQ  
APAKTADTPATSKATIRDLNDPSHVKTLOEKAGKGACTVVAVIDAGFDKNHEAWRLTDKTKARYQSKENLEKAKKEHGITYGEWN  
DKVAYYHDYSKDGKNAVDQEHGTHVSGILSGNAPSEMKEPYRLEGAMPEAQLLLMRVEIVNGLADYARNYAQAIRDADVNLGAKVIN  
MSFGNAALAYANLPDETCKAFDYAKSKGVSVITSAGNDSSFGKPRLPLADHPDVGVVGTPTAAADSTLVASYSPDKQLTEATATVK  
25 TDDHQDKEMPVISTNRFEPNKAYDYAYANRGTKEDDFKDVEGKIALIERGDIIDFKDKIANAKKAGAVGVLIIYDNQDKGFPIELPNV  
DQMPAFISRRDGLLLKDNPPTITFNATPKVLTPTASGKLSRFSSWGLTADGNIKPDIAAPGQDILSSVANNKYAKLSGTSMSAP  
LVAGIMGLLQKQYETQYPDMTPSERLDAKKVLMSSATALYDEDEKAYFSPRQQGAGDAKKASAATMYVTDKDNTSSKVHLNNV  
SDKFETVTVHNKSDKPQELEYQVTFQTDKVDGKFALAPKALYETSWQKITIPANSSQVTFPVIDASRFSKDLLAQMKNGYFLEG  
30 FVRFKQDPDKTKEELMSIPTYIGFRGDFGNLSALEKPYIYDSKDGSSYYHEANSDAKDQLDGDQLQFYALKNNFTALTTESNPWVIIKAV  
KEGVENIEDIESSETETIFAGTFAKQDDDSHYYIHRHANGKPYAAISPNGDNRDVQFQGTFLRNKALVAEVLDKEGNVWVTS  
EVTEQVVKNYNNDLASTLGSTRFEKTRWDGKDKGKVANGTYTYRVRYTPISSGAKEQHTDFDVIVDNTTPEVATSATFSTEDSR  
LTLASKPKTSQPVYRERIAYTYMDEDLPTTEYISPNEDEGFTLPEEAEETMEATVPLKMSDFTYVVEDMAGNITYTPVTKLLEGHS  
NKPEQDGSDQAPDKKPEAKPEQDGSGQTPDKKETKPEKDSSGQTPGKTPQKGQSSRTLEKRSSKRALATKASTRDQLPTNDKDT  
35 NRLHLLKLVMTTFFLG

The nucleotide and amino acid sequences of GBS 305 in Ref. 3 are SEQ ID 207 and SEQ ID 208. These sequences are set forth below as SEQ ID NOS 13 and 14:

## SEQ ID NO. 13

40 ATGGGACGAGTAATGAAAACAATAACAACATTGAAAATAAAAGTTTAGTCCTGGTTAGCACCGATCTGGAGAACGTCGTC  
ACGTTGTTAGCTAAGTTAGGAGCAATAGTGCAGTTAATGATGGCAACCCATTGATGAAATCCACAGCACAGTCCTTGTG  
AAGAGGGTATTAAGTGGTTGTGGTAGTCATCCTTGAATTGTTAGATGAGGATTTTGTACATGATTAACCTCAGGAATA  
CCTTATAACAATCCTATGGTCAAAAGCATTAGAAAAACAAATCCCTGTTGACTGAAGTGGAAATTGACATACTTAGTTCTAGA  
ATCTCAGCTAATAGTATTACAGGCTCTAACGGAAAACGACAACGACAACTGAGATTGCAAGAAGTCCTAAATGCTGGAGGTCAGA  
GAGGTTGTTAGCTGGGAATATCGGCTTCTCTGCTAGTGAAGTTGTCAGGTGCGAATGATAAAAGACTCTAGTTATGGAATT  
45 TCAAGTTTACGCTAATGGGAGTTAAGCAATTCTGCTCTCATATTGCACTAATTACTAAATTGCAACTCATTTAGATTATCA  
TGGGTCTTGTGAGATTATGTTGCTGCAAATGGAATATCCTAAATGTCCTCATCTGATTTTGGTACCTTAATTTTAATC  
AAGGTATTCTAAAGAGTTAGCTAAACTAAAGCAACAATGTTCTCTACTACGGAAAAAGTTGATGGTCTTACGTA  
CAAGACAAGCAACTTTCTATAAAGGGAGAATATTATGTCAGTAGATGACATTGGTCTCCAGGAAGCCATAACGTAGAGAATGC  
50 TCTAGCAACTATTGCGGTTGCTAAACTGGCTGGTATCAGTAATCAAGTTATTAGAGAAACTTTAAGCAATTGGAGGTGTTAAC  
ACCGCTTGCACACTCGGTAGGTTCTAGGTTCTATAACGACAGCAAGTCACAAATATATTGGCAACTCAAAAGCA  
TTATCTGGCTTGTATAACTAAAGTTCTCTAACTGGCAGGGCTTGTGATCGCCGATATGAGTTGATGAAATTGATACCAAGATAT  
CACTGGACTTAAACATATGGTTGGTTAGGGGAATCGGCATCTGAGTAAACCGTCTGCAACAAAAGCAGGAGTAACCTTATAGCG  
ATGCTTCTAGATGTTAGAGATGCGGTAACATAAGCTTATGAGGTGGCAACACAGGGCGATGTTCTTGTAACTCCTGCAAATGCA  
55 TCATGGGACATGTATAAGAATTGCAAGTCCGGTGTGATGAATTCTGAAACTCTTAGAGGAG

## SEQ ID NO. 14

MGRVMKTITTFENKKVLVGLARSGEAAARLLAKLGAIVTVNDGKFDENPTAQSLLEEGIKVVCGSHPLELLDEDFCYMIKNPGI  
PYNNPMVKKALEKQIPVLTVELAYLVSESQLIGITGSNGKTTTTMIAEVLNAGGQRGLLAGNIGFPASEEVVQAANDKDTLVMEI  
60 SSFQLMGVKEFRPHIAVITNLMPHTLDYHGSFEDYVAKWNIQNMSSSDFLVLFNQGQISKELAKTTKATIVPFSTTEKVDGAYV  
QDKQLFYKGEMISVDDIGVGPSHNVENALATIAVAKLAGISNQVIRETLSNFCCVHKRLQSLGKVGHGIFSYNDSKSTNLATQKA  
LSGFDTKVILIAGGLDRGNEFDELIPDITGLKHMVVLGESASRVKRAAQKAGVTYSDALDVRDAVHKAYEVAQQGDVILLSPANA  
SWDMYKNFEVRGDEFIDTFSLRGE

The nucleotide and amino acid sequences of GBS 313 are in Ref. 3 are SEQ ID 4089 and  
65 SEQ ID 4090. These sequences are set forth as SEQ ID NOS 15 and 16 below:

**SEQ ID NO. 15**

ATGAAACGTATTGCTGTTAACTAGTGGTGGTGACGCCCTGGTATGAACGCTGCTATCCGTGCAAGTGTTCGTAAAGCAATTCTGAAGGTATG  
 5 GAAGTTACGGCATCAACCAAGGTACTATGGTATGGTACAGGGATATTTCCCTTGGATGCTAATTCTGTGGGGACTATCAACCGTGGA  
 GGAACGTTTTACGTCAGCACGTATCTGAATTGCTGAACCTGAAGGTCACTGAAGCTAAAGGGATTGAACAGCTAAACACGGTATTGAAGGT  
 GTAGTAGTTACGGTGGTGATGGTTCTTATCATGGTGCATGCGCTAACCTGAGCAGCGTTCCAGCTGGTACGGTACAATTGATAAC  
 10 GATATCGTTGGCACTGACTATACTATTGGTTGACACAGCAGTGGCACAGCAGTTGAGAATCTGACCGTCTTCGTGATACATGAGCAAGTCAT  
 AACCGTACTTTGGTGTGAGGTATGGAAAGAAATGCAGGAGATATCGCTCTTGGTCAGGTATCGCTGCAGGTGCAGATCAAATTATTGTCCT  
 GAAGAAGAGTTCAATATTGTAAGGTTCTCAATGTTAGAGCTGGTATGGAAACATCACCAAATCATGTCCTTGCAAGAAGGTGTT  
 ATGAGGGTGTGATGGTACGGTACGGAGCAGCAGGACGATAGCGATCTCGTGTGACGAATTAGGACATCTGCTCCGTTGGTAGT  
 15 CCGACGGCTCGTGTGATCGTCTAGCATCTCGTGTGAGCTGGCTGGTCAATTGTTGAGAAGGGTGTGTTAGCCGTTGGTCCAC  
 AACGAGAAATGGTGAAGTCCAATTAGGTTAGCAGAAGAAGGTGTTAGCTGACTGATGAAGGAAAATCGTTGTTAATAATCCG  
 CATAAAGCGGACCTCGCTGGCAGCCTTAATCGTGCACCTGCCAACCAAAGTAGTAA

**SEQ ID NO. 16**

15 MKRIAVLTSGGDAPGMNAAIRAVVRKAISEGMEVYGINQGYGMVTGDFPLDANSVGDTINRGGTFLRSARYPEFAELEGQLKGIEQLKKHGI  
 VVIVGGDSYHGAMRLTEHGFPAVGLPGIDNDIVGTDYTIGDFTAVATAVENLDRLRDTASHNRTFVVEVMGRNAGDIALWSGIAAGADQIIVP  
 EEEFNIDEVVSNVRAGYAAGKHHQIIVLAEGVMSGDEFAKTMKAAGDDSDLRVTNLGHLLRGSPARDRVLASRMGAYAVQLLKEGRGLAVGVH  
 NEEMVESPIGLAEGGALFSLTDEGKIVVNNPHKADRLAALNRDLANQSSK

20 The nucleotide and amino acid sequences of GBS 322 in Ref. 3 are SEQ ID 8539 and SEQ  
 ID 8540. These sequences are set forth below as SEQ ID NOS 17 and 18:

**SEQ ID NO. 17**

ATGAATAAAAGGTACTATTGACATCGACAATGGCAGCTTCGCTATTATCAGTCGAAGTGTCAAGCACAAGAAACAGATA  
 CGACGGTGGACAGCA  
 25 CGTACTGTTTCAGAGGTAAGGCTGATTTGGTAAAGCAAGAACATAATCATCATACTGTTGAAATATCTGTGATACACTAAGCGTTATTTCAGAA  
 GCAATGTCATTGATGAATGCTTACGAAAAAAATAACATTCGAGATATCAATCTTATTATCTGAGACAACACTGACAGTAACTTACGAT  
 CAGAAGAGTCATCTGCCACTTCATGAAAGGTTCTCAATACAATTTCGAGGTTGACACCAGAGCAGCAACAACAGATTGTTG  
 30 CCAATGAGCTACTGCTGAGACAAAAAGTTCTCTCAATACAATTTCGAGGTTGACACCAGAGCAGCAACAACAGATTGTTG  
 TCTTCGTCAGCAGCTTGAATACAAAGAGGAGTACAGCAGGAGCTGTTAGTCAAGCAGCAGCTAATGAACAGGTTACCAAGCTCTGTG  
 AAGTCGATTACTCAGAAGTCCAGCAGTAAAGAGGAAGTTAACCAACTCAGACGTCAGTCAGTCAACAAACAGTATCACCAGCTCTGTG  
 35 GCCGCTGAAACACAGCTCCAGTAGCTAAAGTAGCAGCACCGGTAAGACTGAGCACGCCCCTAGTGGCAAGTGTAAAGTAGTC  
 GACTCTCAAAGTA  
 GAAACTGGTCATCACCAGAGCATGTCAGCTCCAGCAGTCTCTGTGACTACGACTTCACAGACAGTAAGTTACAAGCGACTGAAGTT  
 AAGAGCGTTCCGGTAGCACAAAAGCTCCAACAGAACACCAGTAGCACAACACAAATCAGTAGCTGACATCTGAAATGCA  
 40 GGGCTCCAACCTCATGTTGAGCTTAAAGAGGAAAGTAGCGTCAATTATGGGTTAATGAAATTCTGACATACCGTGGGGAGATCCAGGTGAT  
 CATGGTAAAGGTTAGCAGTTGACTTATTGAGGTTAATCAAGCAGCTGGTAATAAAGTAGCTGACATCTACACAAAATATGGCAGCAAA  
 45 AACATTCTATGTTATCTGCAACAAAGTTTACTCAAATACAAACAGTATTATGGACCTGCTAATACTGGAAATGCAATGCCAGATCGTGGT  
 GCGCTACTGCCAACACTATGACACGTCACGTTACCTTAACAAATAATAAAAAGGAAGCTATTGGCTTCTTTTATGCTGAAT  
 AGACTTCAAGGTTCTTATATAATTTTTATTA

**SEQ ID NO. 18**

40 MNKVLILTSTMAASLISVASVQAQETDTWTAARTVSEVKADLVQDNKSSYTVKYGDTLSVISEAMSIDMNVLAKINNIADINLIYPETTLTVYD  
 QKSHTATSMKIEPTPTNAAGQTATVDLKTNQSVADQKVSLNTISEGMPTEAATTIVSPMKTYSSAPALKSKEVLAQEQA  
 VSQAAANEQVSPAPV  
 KSI  
 45 KSVPAAKEEVKPTQTSQSTTVSPASVAETPAPVAKVAPVRTVAA  
 PAPV  
 KSVPQA  
 KAPTATPV  
 AQPASTTNA  
 AAHPENAGLQPHVAAYKEV  
 VASTYGV  
 NEFSTYRAGDPGDHGKGLAVDFIVG  
 TNQALGNKVAQY  
 STQNMAAN  
 NISYVIWQKFYSNTNSIYGP  
 ANTNAMPDRGGVTANHYDHVHSFNK

45 The nucleotide and amino acid sequences of GBS 328 in Ref. 3 are SEQ ID 6015 and SEQ  
 ID 6016. These sequences are set forth below as SEQ ID NOS 19 and 20:

**SEQ ID NO. 19**

ATGAAAAGAAAATTATTTGAAAAGTAGTGTCTTGGTTAGTCGCTGGGACTCTATTATGTTCTCAAGCGTGTCCGCGACCAAGTCGGTGT  
 50 CAAGTTATAGCGTCATGACTTTCATGGTCACCTGACAATACTGAAACAGCAAATATGCCATGGAAAGTTGCTAATGCTGGTACTGCTGCT  
 CAATTAGATGTTATGGATGACGCTCAAAACAAAGTCAACCTAACCTAATGGTAAAGCATTAGGGTTCAACCGAGGCAATGGTTGGA  
 GCAAGTCGCCAACACTCTGCCCTTCAGATGAACTGTCAGGTTAAAGCTGCTCCAGATTCTAATTAATAATTACGAAATCATCCCACAT  
 55 TTTGATGAAGGTTGGCAGAATATAATCTGTTACTGGTAAAGCCCTGCTCCAGATTCTAATTAATAATTACGAAATCATCCCACAT  
 GAAGCTGCAAAACAAAGAAATTGAGTGGCAAATGTTATTGATAAAAGTTAACAAACAAATTCTCTACAATTGGAAAGCCTACGCTATTAAAATATT  
 CCTGTAATAACAAAAGTGTGAACTGGCTTATCGGGATTGTACCCAAAGACATCCCAACCTTGTCTACGTAACAAATTATGAAACAAATATGAA  
 60 TTTTAGATGAAGCTGAAACGTTCAAGGCTTCTGTTACTGGTAAAGCTGCTCCAGATTCTGCTCCAGATTCTGCTTCTGTTGATCAAGCATT  
 AGTAAAATGATATTGCTGAAGGTAAGCAGCAGAAATGATGAAAAGTCGAAACTCTGTTCTGCTCCAGATTCTGCTCCAGATTCTGCTTCTGCT  
 CACAATCATCAATACAAATGGCTTGTGAAAACCTCGTATTGTCAGCAGCTCTCAAGGAAAAGCCTATGCTGATGTCAGCTGCTTCTGCT  
 GCTTCTGCT  
 65 GATACTGATACACAAGATTTCATTGAGACCCCTCGCTAACAGTAATTGCAAGTGTGCTCCCTGGTAAAAAAACAGGTAGTGCCTGTTGATCAAGCATT  
 GTGACCAAGCTAACACTATCGTTAAACAAAGTAACAGAACAGCTAAATTGGTACTGCGAGGTAAGTGTCTGCTGCTTCTGTTGATCAAGCATT  
 AATGTTAGTCCGGTAGGCAGCTCATCACAGGGCTAACACTAGCAATTGCTGCAAAAGCTGCCAGATATGATTGTTGCTGCTGCT  
 GGCATTGCTGCTGACTTACTCATCAAACAGATGGAACAATCACCTGGGGAGCTGCACAAGCAGTTCAACCTTTGGTAAATATCTAACAGTCGTC  
 GAAATTACTGGTAGAGGATCTTATAAAGCACTCAACGAACAATACGACCAAAACAAACAAATTCTCCCTCAAATAGCTGGTCTGCGATACACTTAC  
 ACAGATAATAAAAGAGGGCGGGAAAGAAACACCAATTAAAGGTTAAAGGCTTATAATCAATGGTAGGAAATCAATCTGATGCAAAATACAAA  
 TTAGTTATCACTGACTTATTGAGTAAAGAGGTTAAAGGCTTCAAGGTTGAGCTTCAAGGTTGAGGCAATTAAACCTTACAGTCACTATG  
 GAGGTTAAT  
 75 GAAACTATTACACAAATGATGGTACACATAGCATTAAAGAACATTATTAGATCGACAAGGAAATTGAGCACAAGAGATTGATCAGAC

ACTTTAAACCAACAAAATCTACAAAAATCAACCCTGTAACCTACAATTCAACAAAACAATTACACCAATTACAGCTATTACCCCTATG  
AGAAATTATGGCAAACCATCAAACCTCAACTGTAAAATCAAACAACTCTGAATATGGACAATCATTCTTATGTCTGTC  
TTGGTGTGGACTTATAGGAATTCTTAAATACAAAGAAAACATATGAAA

**5 SEQ ID NO. 20**

MKKKIIILKSSVVLGLVAGTSIMFSSVFADQVGVQVIGVNDFHGALDNTGTANMPDGKVNAGTAAQLDAYMDDAQKDFKQTNPNGESIRVQAGDMVG  
ASPANSGLLODEPTVKNFNAMNVBYGTLGNHEFDEGLAEYNRIVTGKAPADSNINNITKSPHEAKQEIVVANVIDKVNQIIPWNKPYAIKN  
PVNNKSVNVGFFIGIVTKDIPNLVLRKNYEQYEFLEAETIVKYAKELQAKNVKAIVVLAHVPATSKNDIAEGEAAEMMKVNVQLFPENSVDIVFAG  
HNHQYTNGLVKGKTRIQLAQSGKAYADVRGVILDQDFIETPSAKVIAPGKKTGSADIQAIVDQANTIVKQVTEAKIGTAEVSVMITRSVDQD  
10 NVSPVGSEETPKVVKARKSNSWPDIDFAMTNNGGIRADLLIKPDTITWGAAQAVQPFGNILQVVEITGRDLYKALNEQYDQKQNFFLQIAGLRYT  
TDNKEGGEEETPKVVKARKSNSWPDIDFAMTNNGGIRADLLIKPDTITWGAAQAVQPFGNILQVVEITGRDLYKALNEQYDQKQNFFLQIAGLRYT  
ETITQNDGTHSIKKYLDRQGNIVAQEIISDNLNQTKSKSTKINPVTTIHKKQLHQFTAIPMRNYGKPSNSTTVKSQLPKTNSEYQGSFLMSV  
FGVGLIGIALNTKKHHMK

15 The nucleotide and amino acid sequences of GBS 330 in Ref. 3 are SEQ ID 8791 and SEQ  
ID 8792. These sequences are set forth below as SEQ ID NOS 21 and 22:

**SEQ ID NO. 21**

ATGAATAAACCGCTAAAAATCGTTGCAACACTTGGCTCTGCCGTTGAATTCCTGGTGGTAAGAAGTTGGTAGCTGGATACTGGGGTGAAGC  
20 CTTGACCTAGAAGCTTCAGCAGAAAAATTGCTCAATTGATTAAAGAAGGTGCTAACGTTTCCGTTCAACTTCTCACATGGAGATCATGCTGAG  
CAAGGAGCTCGTATGCCCTACTGTTCTTAAAGCAGAAGGAGATTCCAGGAAAAAGTGGCTCCCTCTGATACTAAAGGACCTGAAATTCTGACA  
GAACCTTTGAGATGTTGCTGGACTTCCATTCTATACAAACAGTACAAATTACGTTGCTACTAACGAAAGGTATCAACTCAGAGTC  
ATTGCAATTGAGATGTTGCTGGACTTGCACATCTTGTATGACCTTGAAGTTCAGTTGCTTAAGCCTTGTGAAATCCCTTATTGGTAAACAAAAAGGTGTAACATCCCTTATACTAAA  
25 TTTGCAAAAGATAAAAGACACTCGTGAAATTGAAAGTAGTTGTTGAGAATGATGCCCTTATTGGTAAACAAAAAGGTGTAACATCCCTTATACTAAA  
ATTCCCTTCCCAGACTTGCAGAACCGCAGATACTGCTGATATTGCCCTTATTGGACTTGAAGGACTTAACTTTGCTATCTCATTGTTGACGTACT  
GCTAAAGATGTTAATGAGTTCTGTGCTATTGTTGAGAAGAAACTGGSMATGGACACGTTAACGTTAAGTGTGTTGCTAAATTGAAATCAACAGGTATCGAT  
30 AATATTGAGATGAGATTATCGAAGCAGCAGATGGTATTATGATTGCTCTGTGGTGTATGGGTTGCAAGTTCATTTGAAATGGTTCCAGTTACCAA  
AAAATGATCATTACTAAAGTTAATGCAGCTGGTAAAGCAGTTATTACAGCAACAAATATGCTGAAACAATGACTGATAAACACCAGTGCAGCTCGT  
TCAGAGATATCTGATGCTCTCAATGCTGTTATTGATGGTACTGATGCTAACATGCTTCAAGCTGAGTCAACTGTAATACCCAGTTGACTCA  
35 GTTCGTTAACATGGCTACTGATAAAATGCTCAAACATTACTCAATGGTATGAGTGGCTTCAAGTGTGCTAACATGCTGCAATTCCCACGTAATAACAAACACT  
GATGTTATTGCACTGCGTTAAAGATGCAACACACTCAATGGTATCAAACATTGTTGTAACAAATTACTGAAACAGGTATAACAGCTCGTGCCTT  
TCTAAATTCCGTCAGATGCAGACATTGGCTGTTACATTGATGAAAAAGTACAACGTTATTGATGTTAATCTGTTGATGTTAATCTGTTGCTTGCCTT  
GCAGACAAACCGACACTACAGATGATATGTTGAGGTTGCAAGACGTGAGCAGTGAACGAGCAGGATTGTTGAATCAGCGATAATATCGTTATC  
40 GTTGAGGTGTTCTGTAGGTACAGGTGAAACTAACACAATGGCTGTTAA  
VAGVPVGTTGINTMRVRTVK

The nucleotide and amino acid sequences of GBS 338 in Ref. 3 are SEQ ID 8637 and SEQ  
ID 8638. These sequences are set forth below as SEQ ID NOS 23 and 24:

**45 SEQ ID NO. 23**

TTGTCGCTATAATAGACAAAAGTGGTATTTATGTTAGCATTAACTGGTATATCATTAACTCAAACAGATACTTGA  
ACGTGAAACATTCCAACAGTCTTCAGCAACTAATGACCGAACTATCTGATGTTATGGTGAAGAGACTGATTCTCCATTCACTA  
TTACAGCTGGTGTGAAATTCAAGCTTATGAAACCATCAAAAAAGGTATTICAAATTATTGACCATATTCAACTAGCTCTAAAA  
50 CCTGTTAATGTAAGGTTCGCCCTCGGTACAGGAAACATATAACATCCATCAACTCAAAGTGAAGTGGCTGCTGATGGTCTGC  
CTACTGGCAGTCTGCTCAGTATTAACTATGATGTTAAAGTGGAAACAGTTCAAGTGTAGCTATTGCTGCTGATGGTCTGC  
AAGACCAAAACCTGAAATTACACTAAATAGTCTCATTGAGCTGGTATTATGAACTGTTCAAGTCAAATGGACTACAAACCATTTCAA  
ATGCTTGGACTTAAACTTCAAGATAATTATCAAGAACAAATTCAACATCAAAAGTTAGCCAACCTGGAAAATATTGAACCTAG  
TGCCTGACTAAACGCCCTAAAGCAAGCGGTCTGAAGATTACTTAAGAACGAGAACACAGGCAGCCGATCTATTGTTAAAGTT  
55 GCACTCAAACATAAGGGGAAGCTATGATTTC

**SEQ ID NO. 24**

MSAIIDKKVVIFMYLALIGDIINSKQILERETFQQSFQQLMTELSDVYGEELISPFTITAGDEFQALLKPSKKVFQIIDHIQLALKPVNVRFLG  
60 NIITSINSNESIGADGPAYWHARSAINHIDKNDYGTQVVAICLDDDEDQNLELTNSLISAGDFIKSKWTNHFQMLLEHLILQDN  
LENIEPSALT/KRLKASGLKIYLRTTQADLLVKSCTQTKGGSYDF

The nucleotide and amino acid sequences of GBS 358 in Ref. 3 are SEQ ID 3183 and SEQ  
ID 3184. These sequences are set forth below as SEQ ID NOS 25 and 26:

**SEQ ID NO. 25**

ATGTTTATAACAATTGAAGAGCTGGTAGAGCAAGCTAATAGCCAACATAAGGTAACATAGCAGAGCTCATGATCAAACGGAAATTGAAATGACT  
 GGTAGAAGTCGTGAAGAAATTCTTATATTATGTCGGAATCTTGAGTCATGAAAGCTCTGTTATTGATGGATTACCCCTAGTAATCAATC  
 ACTGGTTAACAGCGGTGATGTCAGATGGATCAATATTACAATCAGGAAAACCTATTTCAGATACCACAATCTAGCTGCCGTTAGGAAT  
 GCTATGGCTTAATGAGTTAAATGCTAAGATGGACTGGCTGCAACACCAACTGCAGGTAGTGCAGGATGTTACCAAGCTGTGATTCTAC  
 5 GCCATTGAAAGCTTAATTTAACAGAAGAGGAACTTGATTTCTTACAGCGGCCATTGGCTCGCATGGTAATAATGCCCTATAC  
 TCAGGTGAGAAGGGAGGTGCAAGCTGAGTTGGCTCAGCTGCTGCTGCTGCTTCTAGTTATGGCTGCTGGAGGTACTCTTCCAA  
 GCTAGCAAGCTATAGCATTTGTTAAATGCTGGACTATCTGACCCCTGTTGAGGTTAGTGAAGTCCTGTTGAAAGCGGAAT  
 GCTCTGGATCAAGTTTGCACTTGTGATATGCCCTGGCTGGTATTGAATCGAAATTCCAGTAGATGAAGTTATTGATGCAATGTAT  
 10 CAAGTTGGATCAAGTTACCGACTGCTTCTGAGACTGCAGAAGGAGACTGCTGCCACCCGACAGGAAGACGTTATAGTAAAGAAATTGTT  
 GGGGA

**SEQ ID NO. 26**

MFYTIIEELVEQANSQHKGNIAELMIOETIEMTGRSREEIRYIMSRNLEVMKASVIDGLTPSKSISGLTGDDAVKMDQYLQSGKTISDTTLAAVRN  
 15 AMAVNELNKMLGLVCAPTAGSAGCLPAVI STAIKLNLTTEEQLDFLFTAGAFGLVIGNNAISGAEGCQAEVGSASAMAAAALVMAAGGTPFQ  
 ASQAIAFVKNMGLLICDPVAGLVEVPCVKRNALGSSFALVAADMALAGIESQIPVDEVIDAMYQVGSSLPTAFRETAEGGLAATPTGRYYSKEIF  
 GE

The nucleotide and amino acid sequences of GBS 361 in Ref. 3 are SEQ ID 8769 and SEQ ID 8770. These sequences are set forth below as SEQ ID NOS 27 and 28:

**SEQ ID NO. 27**

ATGAGCGTATATGTTAGTGGAAAGGAAATTATTCCTTGGGAAAGAATTATAGCGAGCATAAACAGCATCTCTGACTTAAAGAAGGAAATT  
 CTAACATTTATATAAAATCACGACTCTATTAGATCTTACAGGAACGATAACTAGTGACCCAGAGGTTCTGACAAATACAAAGATGAGAC  
 ACCTAAATTAAATTGCTTTACCGCTTTGAAGAGGCTCTGCTTCTCAGGTGTTAAATTAAAGCTTATCATATAATTGCTGTGTTTAGGG  
 25 ACCTCTGTTGGGGAAAGAGTGTGGTCAAATGCTCTGCTTACATTGAAAGAGGAGGCTCAAGTGTAGTGTAGTTATTAGAAAAGCATCTG  
 TTTACCATATTGCTGATTGATGGCTTATCATGATATTGTTGGGAGCTTCGATGTTATTCAACGCCCTGTTCTGCAAGTAATAATGCCGTAAT  
 ATTAGGAACACAATTACTTCAAGATGGCATTGTGATTAGCTATTGTTGGGCTGTGATGAGTTAAGTGTATTTCTTAGCAGGCTTCACATCA  
 CTAGGAGCTATTAAACAGAAATGGCATGTCAGGCCATTCTCTGAAAAGGAATCAATTGGGTGAGGGCCTGGTTTGTGTTCTGCAAAG  
 ATCACTCTCTGCTAAATATGGAAAATTATGGTGTCTTACTCTCAGATGGTTATCATATAACGACACCTAACGGCAACAGGTGAAGGGCGGC  
 30 ACAGATTGCAAGCAGCTAGTACTCAAGCAGGTATTGACTACAGTGAGATTGATATTAAACGGTCACGGTACAGGTACTCAAGCTAATGATAAA  
 ATGAAAAAAATATGATGCTAAGTTTCCCAGACAACGACATTGATCAGCAGTACCAAGGGCAACGGGTCAACTCTAGGGGCTCAGGTATTA  
 TCGAATTGATTAATTGTTAGCGGAATAGAGGAACAGACTGTACAGCAACTAAATGAGATTGGGATAGAAGGTTTCCAGAAAATTGTC  
 TCACTAAAGAGAGAAATCCCAATAAGAAATGCTTAAATTCTCTGTTGGGAAATAATAGCTGCTCTATCTGCTATCTGCTATCTGCTA  
 CCTCTAGAAACATTCTGCTAGAGAAAATCTTAAATGCTTATCTCATGTCCTCTCCTAAAGAATGAACTCACTTCTATAACCTATG  
 35 AAAAGGTGCTGATTAATTCACGACTTCAAGCAGTAAACGGCTTAAAGGGCTGAGACCAACCCAAACTGTAACCCAGCAATTAGAAAATGGA  
 TGATTTTCCAAAATGGTGCCTAACACAGCTCAAGCACTAATAGAAAGCAATTAAATCTAAAAAACAGATACTTCAAAAGTAGGAAATTGTA  
 TTTACACACTTCTGGACCGATTGAGGTTGTTGAGGTTATTGAAAGCAACACAGGATGCACTGTTCTGCTTCAACGATTCCCCT  
 TTACAGTAATGATCAGCAGCTGTTGCTTATCTTAAATAACAGCTCTTATCTGCTTCTGCTTAACTAGTGAGGCTTGTGATGG  
 40 TATAACATATGCCAAGGAAATGATGCTAACATGTTGTCGGTCTGATTATTGTCAGCACAAGTCTCTCGTCAGCATTGATAATTCTCTATAATAT  
 TAGGTAGTAAAGATAATAAAATAGCCAAAATCACAGATGCTGAGTATTGTTCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTG  
 AACCAATTAAACTATGATAGTCAATGTTGTCGGTCTGATTATTGTCAGCACAAGTCTCTCGTCAGCATTGATAATTCTCTATAATAT  
 45 AACCATAAAAGATATCAAGGTTCTGTTGGAAATGAGCGGAAGAAGGCAAGGCTAGTTGAGTATTGATGCTGCTGCTGCTGCTGCTGCTG  
 ATGCAAAACCTGCTCTGGTCAAGTTGATTTCTATCTAATGGTGTGCTGAGAAACTGGACTTACTGTTAATGAAAGTATAGAAAAGGCTATT  
 ATTAGTCCTATCTTATTGATCTCGGTGGTATCTCTTGTATTATTGAAAAAGG

**SEQ ID NO. 28**

MSVYVGIGIISSLGKNYSEHKQHFLKEGISKHLYKNHDSILESYTGSITSDEPVPEQYKDETRNFKAFTAEEALASSGVNLKAYHNIAVCLG  
 TSLGKKSAGQNALLYQFEEGERQVDASILLEKASYVHIADEL MAYHDIVGASYVISTACSASNNAVILGTQLLQDQDCDLAI CGGCDELDISI LAGFTS  
 LGAINTEMACQPYSSKGKINLGEGAGFVVLVKDQSLAKYKGKIGGLITSDGYHITAPKPTGEQAAQIAKQLVTQAGIDYSEIDYINGHGTGTQANDK  
 MEKNMYGKFFPTTLISSTKQGTGHTLGAAGIIELINCLAAIEEQTPATKNEIEGFPENFVYHQKREYPIRNALNFSFAFGNNNSGVLLSSLDS  
 50 PLETLPARENLKMAILSSVASISKNESLSITYEKVASFNFDEALRFKGARPPKTVNPQFRKMDDFSVMVTAQALIESNINLKQDTSKVGV  
 FTTLSGPVEVVEGIEKQITTEGYAHVSASRFPFTVMMNAAGMLSIIIFKITGPLSVINSTNGALDIQYAKEMRNDNLDVILVSANQWIDMSFMWW  
 QQLNYDSQMFVGSDDYCSAQVLRSQALDNSPILLGSKQLKYSHKTFDVMTIFDAALQNLLSDLGLTIKDIKGFVNERKKAVSSDYDFLANLSEYYN  
 MPNLASQFGFSSNGAGEELDYTVNESIEKGYYLVSYSIFGGISFAIIIEKR

55 The nucleotide and amino acid sequences of GBS 404 in Ref. 3 are SEQ ID 8799 and SEQ ID 8800. These sequences are set forth below as SEQ ID NOS 29 and 30:

**SEQ ID NO. 29**

ATGAAAATAGATGACCTAACGAAAGCTAACATGTTGAAGATCGTCGCTCCAGTAGCGGAGGTTCACTCTCTAGCGGAGGAAGTGGATTACCGATT  
 60 CTTCACTTTATTGCTGCGAGGGAGTTGAAAACCAAGCTTGTTTAATCATCTACTGCTACTTGGCGAGGGACTAACACGACTTTT  
 AATGACTCATCTCACCTCTAGTACCAATCTCAGAATGCTCAGCTCTGTTGATAATAGCGAACAGAACAAATCGATTTCGTTAATAAA  
 GTCCCTGGCTCAACTGAGGATTCTGGTCAAAAGAATTCCAACCAAGGTTTGGAAATTATAAGGAACCAAAACTTGTCTTTACACCAATTCA  
 ATTCAAAACAGGTGTTGTTATAGGTGAATCTGCTCAGGACCAATTGTTGTCAGCAGATAAAAAAACTATCTGATATTCTCTTCAATGAA  
 TTATCACATAATATGGTGACTCTGGTGTATTGCTATGGCTACGTCATGCCAACGAAGTTGGTCACCCACATTCAAAACAGAGTTAGGCATTATG  
 GATAAGTATAATAGAATGCGACACGGACTTACTAAGAAAGAAGCAATGCTTAAATGTCGGCTAGAACCTCAAGCAGATTATTGCAAGGGGT  
 65 TGGGCTCACTACATCAGGGAAAAAAATCTCTTAGAACAAGGAGACTTTGAGAAGAGGCCATGAATGCTGCCACGCCGTCGGAGACGATACCCCTCAG  
 AAAGAAACCTACGGAAAATTAGTGCCTGATAGCTTACCCATGGAACAGCTGAACACGCCAACGTTGGTTAACAAAGGCTTCAATATGGTAC  
 ATCCAAACACGGTGATATTCTCGGTAGAACATCTA

SEQ ID NO. 30

MKIDDLRKSDNVEDRRSSGGFSSGGGLPILQLLRLRGWSWKTLLVVLII LLLLGGGGLTSI FNDSSSPSSYQSQNVSRSVNDSATREQIDFVNKL  
VLGNSTYDFWSQEFTQGFGNYKEPKLVLVLYTNSI QTGCGIGESASGPFYCSADKKIYLDISFYNELSHKYATGDFAMAYVIAHEVGHHIQTELGIM  
KGYNRMRHGLTKEANALNVRLELQADYYAGVWAHYIRGKNLLEQGDSEEAMNAAHAVGDDTLQKETYGKLVPDSTHTGTABQRQRWFNKGQYGD  
IQHGDTFSVBLH

The nucleotide and amino acid sequences of GBS 656 in Ref. 3 are SEQ ID 9323 and SEQ ID 9324. These sequences are set forth below as SEQ ID NOS 31 and 32:

SEQ ID NO. 31

10 ATGAAAAGATTACATAAACTGTTATAACCGTAATTGTACATTAGGTATGGGGGTAATGACCTTGGCTTCCAACGCCGAAACCGTA  
 ACGCCGATAGTACATGCTGATGTCAATTCTATGTTGATACAGGCCAGGAATTCAAATTAATTITAAATGCTATTGGTAACCTACATTTC  
 TATGTTAATGGTATTTGAAATTAAATATCAGAACAAATTATGCTGATGTCATGTCATTAAAGCGTAGTGTCAAATACATTGACAATCAA  
 CAAAGACTATCAACTGCTAACTGCTGATGAAACCATTCGTCATATCAAATCGCAGAGATACCACCTTCCCGATGCAAAATTGAAA  
 ACCATTAGGTTGGCATCAAGTAGCTACTAATGACCATTATGGACATGCGAGTCGACAAGGGCATTTAATGCTTATGCTTAGCTGAAATT  
 15 TGGGATGCTTCGCGTCAATCTCAAAATGTTGTCACACAAAAGCTCACTTCAACCAATCAAATCAAAATCACTGIGACAAAATTATTAT  
 GAAAGCTTGTGCAAGGCGGTTGACCAAAACAAACGCTGTTACCGTGTAACCTCATTGTACCGTAATGATACTGATTIAGTCCATTGCA  
 ATGCACCTAGAAGCTAAATCACAAAGATGGCACATTAGAATTATGTTGCTATTCAAACACACAAGCATCATACACTATGGATTATGCAACAGGA  
 GAAATAACACTAAAT

20 SEQ ID NO. 32

MKRLLHKLFITVIATLGMLGVMTFGLPTQPQNVTPIVIYHADVNNSVDTSQEBFQQNLKNAIGNLPFQYVNGIYEIENNNTLNADVNVKAYVQNTIDNQYRQSTANAMLDRTIIRQYQNRDRDFTLPPDNWPKLPGHWQVATNDHYGHAVDKGHLJAYALAGNFGKGWDASVSPNPQNVTIQTAAHSNQSQNQKINGQNYY  
ESLVRKAVDQNKVRVYRVTFLYRNDTDLVFPAMHELALESQDGTLEFNVAIPNTQASYTMDTAYCETLNL

25 The nucleotide and amino acid sequences of GBS 690 in Ref. 3 are SEQ ID 9965 and SEQ  
ID.9966. These sequences are set forth as SEQ ID NOS 33 and 34 below:

SEQ ID NO. 33

ATGAGTAAACGACAAAATTAGGAATTAGAAAAAGGAGCAATTATCAGGGCTCTAGTCGCACTAATTGTAGTAATAGGGCTTTTATGG  
30 GTACAATCTCAACCTAATAAAGAGTCAGTAAAACACTAACAAAGTTTTAAATGTTAGGAAAGGAGTGTTCCTCTAACCTTCTGACAGGA  
AAAGCTAAGGCTAATCAAGAACAGTATGTTAGTGTCTAAATGAGGTAATCGAGCACAGTCACTGTTAACAGGTTAAGGGTGATAAAAATCAGCT  
GGTCAGCTTAGTTAATGATACAACAACTGCAACAGCAGCCTACAGCACACTGCTAACATGCTTAATGCTTAATTTAAATAAAGTAGCGCCTCAGATTAAAT  
CTAAAGACAAACAGGAAGTCCTCCAGCTATGGAATCAAGTGATCAATCTCTTCATCATCACAAGGACAAGGGACTCAATCGACTAGTGGTGCAGC  
AATCGTCACAGCAAAATTATCAAAGTCAGCTAAATGCCATACAAACCAAACTCAAGGATTGATGATGCTTATGCGATGCAACAGGCAGAA  
35 GTAAATAAAGCACAAAAGCATTGAAATGATGACTGTGTTATACAAAGTCAGCTATCAGGCCAGCTGGTGTGAAATTAGTGATATTGATCAGCTTC  
AAAACTTAGTCAGTACTGTCCATGAGCAACTGAGGTTAACCTCAAGGATACAAAGGAAAGTCAAGGAGTACTGAGTATTGTTGGCTAATGTTAAAAGAC  
CAGGCTGTTAAAATAAATCTAAGGCTATCTGACAAGGAATGGGAAGTTAAATTCTATATATCTAAATTATCCAGAAGCAGAAAGCAACAAAC  
AATGACTCTAAACGGCTCTAGTCGCTGTTAAATTATAAATTAAGGATGATATTACTAGGCCCTCTGATGCTTAAACAAAGCTTACCTTACCTATCA  
40 GTTGTAGTAGTGTAAATGGAGATAAGGACCTTATGTCCTCAAGGTTACAGGTTCTGATGATAAAACAAAGATAATAAAACACTTGTGTTGGGTATACAAATGCTT  
AATCGTAAATTCTCAAGGTTGAGTCAGGTCAGGTTAAAGGCTAGTCAGGTTCAAGGACAAAGGAAATTGTTAGGGCTTACAGGTTGAAAGCAGGAAATCGTGGTT  
ACTAATCCAGTAAACCTCTCAAGGATGGCAAAAAATTGATAATATTGAAATCAATCGATCTTAACCTTAATAAGAAAATCAGAGGTGAAA

SEQ ID NO. 34

MSKRQNLLGISKKGAIISGLSVALIVVIGGLWVQSQSPNKSAVKTNVKVFNRREGSVSSSTLLTGKAKANQEQQYVYFDANKGNRATVTVKVGDKITAG  
45 QQLVQYDTTTAQAAAYDTANRQLNKVARQINNLKTTGSLPAMESSDQSQQGQGTQSTSQTGATNRLQQNYQSQANASYNQQLQDLNDAYADAQAEVN  
KAQKALNDTVITSDVSGTVEVNEQNSIDPASKTSQVLVHVATEGKLQVQGTMSEYDLANVKKDQAVKI KSKVYPDKEWEKGKISYI SNEYPEAEANNNDS  
NNGSSAVNYKVKVDITSPLDAKLQGFTVSVEVNGDKHLIVPTSSVINKDNKHVFVVYNDSNRKISKVEVKIGKADAKTQEILSGLKAGQIVVTNP  
KTFKDQGKIDNIESIDLNSNKKSEVK

The nucleotide and amino acid sequences of GBS 691 in Ref. 3 are SEQ ID 3691 and SEQ ID 3692. These sequences are set forth as SEQ ID NOS 35 and 36 below:

SEQ ID NO. 35

ATGAAAAAAATTGGAAATTATTGTCTCACACTACTGACCTCTTTGGTATCTGGCGGACAACAAACTAACAGAAGCACTAAAACAACATT  
55 TCTAAAATGCCAAAATTGAAGGCCTCACCTATTATGGAAAAATTCCGAAAATCCGAAAAAGTAATTAAATTTCATATTCTTACACTGGGTAT  
TTATTAAAATCTAGGTGTTAATGTTCAAGTTCAGTTAGAGTAAACACTGGGTTTGGTAAAGACTGCCCCAGAAAAGTCAAAAAAATTAA  
ACTGCTGTGATGATCACAGAAGCTATTGCGCACAACAAACCTGATTAACTGGTTTGCATCAAGATCCTAACATACTCTGAAAATTGCA  
CCAACTTTAGTTAATTAAATGGTCGACAAAATTATTAGATGATGTCAGCCTTGGGGAAAGTATTCGGTAAGAAAAGAGCTAACATCGTGG  
GTTAGCCAATGGAAAACCTAAACTCTCGCTGTCAAAAAAGATTACACCATATCTAAAGCCTAACACTACTTTACTATTATGGATTTCATGAT  
AAAAAATCTATTATATGGTAATAATTGGACGCGGTGGAGAACCTATCTATGATTCTAGGTTATGCTGCCCTGGAGAAAAGTCAAAAAAAGAT  
60 GTCTTTAAAAGGGTGGTTACCGTTCTGCAAGAAGCAATCTGGTATTACGGTGGAGATTACGGCTTGTAAATATAACAAAACAGACTAAAAAA  
GCAGCTTCATCCTAAAGGAGTGTGCTGGAGAAATTACAGCTGTCAAAAGGGCACATCATGAAAGTAACCTACGAGCTGTTTATTC  
TCGACCCCTCATCTTAAAGGAGCTAACATTAAACAGCTACAAAGGAAATTACAA

SEO ID NO. 36

MKKIGI IIVLTLTFFLVSCGQQTKQESTKTTISKMPKIEGFTYYGKIPENPKVINFNTSYTGYLKLGVNVSSYSLDLEKDSPVF  
GKQLKEAKKL TADDTEAIAAQPKDLIMVFDQDPNINTLKKIAPTLVVIKYGAQNYLDMMPALGKVGKEKEANQWVSQWKTTLAVK  
KDLHHILKPNTTFIMDFYDKNIYLYGNFGRGGELIYDSLGYAAPEVKKDVFKKGWFTVSQEAIGDYVGDYALVNINKTTKAA  
SSLKESDVWKNLPAVKKGHIESNYDVFYPSDPLSLEAQQLKSFTKAIKENTN

5

Other preferred polypeptide antigens include: GBS4 (SEQ ID 2 from Ref. 3); GBS22 (SEQ ID 8584 from Ref. 3); and GBS85 (SEQ ID 216 from Ref. 3), including polypeptides having amino acid sequences with sequence identity thereto *etc.*

The polypeptide is preferably not a C protein (alpha or beta or epsilon) or a R protein (Rib).

10

The nucleotide and amino acid sequences of GBS 4 in Ref. 3 are SEQ ID 1 and SEQ ID 2.

These sequences are set forth below as SEQ ID NOS 37 and 38:

#### **SEQ ID NO. 37**

ATGAAAAGTAAAAATAAGATTTAACGATGGTAGCACTTACTGTCTTAACATGTGCTACTTATTCACTAATCGGTTATGCTGATACAAGTGATAAGA  
ATACTGACACGGAGTGTGACTACGACCTTATCTGAGGAGAAAGATCAGATGAACTAGACCCAGTCAGTACTGGTTCTCTCTGAAAATGAATC  
15 GAGTTCATCAAGTGAACAGAAACAAATCCGTCAACTAATCCACCTACAACAGAACCATCGAACCCCTCACCTAGTGAAGAGAACAAAGCCTGATGGT  
AGAACGAAAGACAGAAATTGGCAATAAAGGATATTCTAGTGGAACAAAAGTATTAAATTTCTAGAAGATGATATTAAAGAATTGTTAGTAAGGCAAGTA  
GTGATCAAGAAGAAGTGGATCGCGATGAATCATCTTCAAAAGCAAATGATGGGAAAAGGCCACAGTAAGCCTAAAAGGAACTTCTCAAAAC  
AGGAGATAGCCACTCAGATACTGTAATAGCATCTACGGGAGGGATTATTCTGTTATCATTAAGTTTACATAAAGAAAATGAAAATTAT

20

#### **SEQ ID NO. 38**

MKVKNKILTMVALTVLTCAKYSSIGYADTSKNDTDSVVTTLSEEKRSDELDQSSTGSSENESSSSSEPETNPSTNPPTEPSQPSPEENKPDG  
RTKTEIGNNKDISSGTKLISEDSIKNFSKASSDQEVRDESSSKANDGKGHSKPKKELPKTDHSHTDVIASTGGI ILLSLSFYNKKMKLY

25

The nucleotide and amino acid sequences of GBS 22 in Ref. 3 are SEQ 8583 and SEQ ID 8584. These sequences are set forth below as SEQ ID NOS 39 and 40:

#### **SEQ ID NO. 39**

ATGAAAAGGATA CGGAAAAGCCTTATTTGTTCTGGAGTAGTTACCCCTAATTGCTTATGTGCTTGTACTAAACAAAGCCAGCAAAAAATGGCT  
TGT CAGTAGT GACTAGCTTTATCAGTATTTCCAGTATTTCAAGAAAGCAGTTCTGGTGAATGATATAAAATGATTCGATCACAGTCAGGTAT  
TCATGTTTGAACCTTATCAGTGTGCTGCCATTATGATGCTGATCTTATCTTCTTATCCTGCACACACTAGAAGCCTGGCGAGACGT  
30 TTGGAACCTAGTTGCACTCTAAAGTCTGTAATTGAGCTTCAAAAGCTATGACTTTGGATAAAAGCTTATGGCTTAGAAGATGTTAGAGGAG  
AAAAAGGAGTAGATGAGTCACCTGTATGACCCCTCACACTTGGAAATGACCCCTGTAAAAGTATCTGAGGAAGCACAACCTATCGCTACACAATTG  
AAAAAGGATCTAAAAGCTAAAGGTTTACAAAAAAATGCTGATCAATTGTAAGGCAATGGCTATTGAGAGAAGTATAACCCAAAATT  
AAAGCTGAAAGCTAAATTTGTCACATACAGCACTCTAGCTAAGCGATACCGGATGACTCAGTTAGGTATTGAGGTGTCT  
35 CAACCGAGAAAGAACCTAGTGTCAAAATAGCCGAAATTCAAGGAGTTGTGAAAACATAAAGGTTAAGACTATTGTTGAAGAGGGAGTC  
ACCTAAATTAGCTCAAGCAGTAGCTCAGCTACTCGAGTTAAATTGCAAGTTAACGAGTTCCCACAAATAAGATTACTTA  
GAAAATTGGAACATAATCTAAGGTACTTGTCAAATCGTTAAATCAATAG

#### **SEQ ID NO. 40**

40

MKRIRKSLIFVLGVVTLICLCACTKQSQQKNGLSVVTSFYPVYSITKAVSGLNDIKMIRSQSGIHGFEPSSSDVAIYDADLFYHSHTLEAWARR  
LEPSLHHSKVSVIEASKGMLDVKHGLEDEVAEKGVDESTLYDPTHWNDPVKVSEEAQLIATQLAKKDPKNAKVYQKNADQFSKAMAIAEKYKPKF  
KAAKSKYFVTSHTSYLAKRGLTQLGIAGVSTEQEPSAKKLAETQEFVKTIFVVEGVSPKLAQAVASATRVKIASLSPXAVPKNNKDYL  
ENLETNLKVLVKSLNQ

45

The nucleotide and amino acid sequences of GBS 85 in Ref. 3 are SEQ ID 215 and SEQ ID 216. These sequences are set forth below as SEQ ID NOS 41 and 42:

#### **SEQ ID NO. 41**

ATGCCTAAGAAGAAAATCAGATACCCCAGAAAAAGAAGAAGTTGCTTAACGGAATGGCAAAGCGTAACCTGAAATTAAAAACGCAAAGAAG  
ATGAAGAAGAACAAAACGTATTAACGAAAAATTACGCTTAGATAAAAGAAGTAAATTAAATATTCTCTCTGAAAGAACCTCAAAACTACTAA  
50 AATTAAAGAAGCTCATTTCAAAAGATTTCAAGAACCTAAGATGAAAAGAACAGAAAAAGAAAAAGAAAAAGAAAAATAGTCACACAGCTAGCCAAAACAACTAATCGC  
ATTAGAACTGCACCTTATTTGTTAGTAGCATTCTAGTCATTTAGTTCCGTTTCTCTACTAATCCTTTAGTAAGGAAAAACAAATAACAGTTA  
CTGGAATCAGCATACACCTGTGATATTGATAGAGAAAACGAAATATTCAAAAAAAACGATTATTCTTCTTAAATTAAACATAAAGCTAT  
TGAACAACGTTAGCTGAGAGATGTATGGTAAAACAGCTAGATGACTTATCAATTCCATAATTCAAGTTCAAGAAAATAAG  
ATTATTGCAATATGCACATACAAAAGCAAGGATATCAACCTGCTGGAAAAGCTGGGATCTGTAATAGTTCAAGGCTACCCAAAGC  
55 TCTTAAACAATTAAACCTTGTAAAGGAAGATAGTATTAAAGCTATTAAAGGTTAACGCTTGTGATTTAGACCCCTGATTAAATTAAGTGAAGATTCAGGTGAT  
AAGTTTAGCTGATTCTAAACGACACCTGACCTCTCTGTTAGATATGCAACGATGGAAATAGTATTAAAGATAACCAATTCTAAATTAAAGAAA  
CTTCCTTTTACAAACAAATTAAAGAAGAACCTTAAGGAACCTCTATTGTTGATATGGAAAGTGGGAGTTACACAACAAATACCAATTGAATCAA  
CCCCCTGTTAAAGCAGAAGATACAAAAATAATCAACTGATAAAACACAAACACAAAATGTCAGGTTCCGGAAAATGTCAGAGCAGAACAAATAA  
CTCAAATACTAATCAACAAGGACAACAGATAGCAACAGAGCAGGCACCTAACCTCAAATGTTAAT

**SEQ ID NO. 42**

MPKKSDTPEKEEVVLTEWQKRNLEFLKKRKEDEEEQKRINEKLRLDKRSKLNISSPPEPQNTTKIKKLHFPKISRPKIEKKQKKEKVNSLAKTNR  
5 IRTAPIFVVAFLVILVSFLLTPFSKQKTTIVSGNQHTPDDILIEKTNIQKNDYFFSLIFKHKAIEQRLAEDVVVKTAQMTRYQFPNKFHIQVQBNK  
IIAYAHTKQGYQPVLETGKKADPVNSSELPKHFLTINLDKEDSIKLLIKDLKALDPDLISEIQVISLADSKTTPDLLLDMHDGNSIRPLSKFKER  
LPFYKQIKKNLKEPSIVDMEVGVTNTIESTPVKAEDTKNKSTDKTQTQNGQVAENSQQQTNNSNQQGQIATEQAPNPQNVN

GBS polypeptides of the invention may be present in the composition as individual separate polypeptides. It is preferred, however, that two or more (*i.e.* 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 10 15, 16, 17, 18, 19 or 20) of the antigens are expressed as a single polypeptide chain (a ‘hybrid’ polypeptide). Hybrid polypeptides offer two principal advantages: first, a polypeptide that may be unstable or poorly expressed on its own can be assisted by adding a suitable hybrid partner that overcomes the problem; second, commercial manufacture is simplified as only one expression and purification need be employed in order to produce two polypeptides which are both antigenically 15 useful.

The hybrid polypeptide may comprise two or more polypeptide sequences from the first antigen group. Accordingly, the invention includes a composition comprising a first amino acid sequence and a second amino acid sequence, wherein said first and second amino acid sequences are selected from a GBS antigen or a fragment thereof. Preferably, the first and second amino acid 20 sequences in the hybrid polypeptide comprise different epitopes.

The hybrid polypeptide may comprise one or more polypeptide sequences from different GBS serotypes. Accordingly, the invention includes a composition comprising a first amino acid sequence and a second amino acid sequence, said first amino acid sequence and said second amino acid sequence selected from a GBS serotype selected from the group consisting of serotypes Ia, Ib, 25 Ia/c, II, III, IV, V, VI, VII and VIII. The first and second amino acid sequence may be from the same GBS serotype or they may be from different GBS serotypes. Preferably, the first and second amino acid sequence are selected a GBS serotype selected from the group consisting of serotypes II and V. Most preferably, at least one of the first and second amino acid sequences is from GBS serotype V. Preferably, the first and second amino acid sequences in the hybrid polypeptide comprise difference 30 epitopes.

In one embodiment, the hybrid polypeptide comprises one or more GBS antigens from serotype V. Preferably, the hybrid polypeptide comprises a first amino acid sequence and a second amino acid sequence, said first amino acid sequence and said second amino acid sequence comprising a GBS antigen or a fragment thereof selected from the group consisting of GBS 80, GBS 35 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691. Preferably, the GBS antigen or fragment thereof is selected from the group consisting of GBS 80 and GBS 691. Preferably, the first and second amino acid sequences in the hybrid polypeptide comprise difference 30 epitopes.

Hybrids consisting of amino acid sequences from two, three, four, five, six, seven, eight, nine, or ten GBS antigens are preferred. In particular, hybrids consisting of amino acid sequences from two, three, four, or five GBS antigens are preferred.

Different hybrid polypeptides may be mixed together in a single formulation. Within such combinations, a GBS antigen may be present in more than one hybrid polypeptide and/or as a non-hybrid polypeptide. It is preferred, however, that an antigen is present either as a hybrid or as a non-hybrid, but not as both.

Preferably, the GBS antigen in one of the hybrid polypeptides is GBS 80 or a fragment thereof. Accordingly, examples of two-antigen hybrids for use in the invention may comprise: (1) GBS 80 and GBS 91, (2) GBS 80 and GBS 104, (3) GBS 80 and GBS 147, (4) GBS 80 and GBS 173, (5) GBS 80 and GBS 276, (6) GBS 80 and GBS 305, (7) GBS 80 and GBS 313; (8) GBS 80 and GBS 322, (9) GBS 80 and GBS 328, (10) GBS 80 and GBS 330, (11) GBS 80 and GBS 338, (12) GBS 80 and GBS 358, (13) GBS 80 and GBS 361, (14) GBS 80 and GBS 404, (14) GBS 80 and GBS 404, (15) GBS 80 and GBS 656, (16) GBS 80 and GBS 690, and (17) GBS 80 and GBS 691.

15 Preferably, a two-antigen hybrid for use in the invention comprises GBS 80 and GBS 691.

Hybrid polypeptides can be represented by the formula  $\text{NH}_2\text{-A}\text{-}\{\text{-X-L-}\}_n\text{-B-COOH}$ , wherein: X is an amino acid sequence of a GBS antigen or a fragment thereof; L is an optional linker amino acid sequence; A is an optional N-terminal amino acid sequence; B is an optional C-terminal amino acid sequence; and n is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15.

20 If a -X- moiety has a leader peptide sequence in its wild-type form, this may be included or omitted in the hybrid protein. In some embodiments, the leader peptides will be deleted except for that of the -X- moiety located at the N-terminus of the hybrid protein *i.e.* the leader peptide of  $X_1$  will be retained, but the leader peptides of  $X_2 \dots X_n$  will be omitted. This is equivalent to deleting all leader peptides and using the leader peptide of  $X_1$  as moiety -A-.

25 For each n instances of {-X-L-}, linker amino acid sequence -L- may be present or absent. For instance, when -n=2 the hybrid may be  $\text{NH}_2\text{-X}_1\text{-L}_1\text{-X}_2\text{-L}_2\text{-COOH}$ ,  $\text{NH}_2\text{-X}_1\text{-X}_2\text{-COOH}$ ,  $\text{NH}_2\text{-X}_1\text{-L}_1\text{-X}_2\text{-COOH}$ ,  $\text{NH}_2\text{-X}_1\text{-X}_2\text{-L}_2\text{-COOH}$ , etc. Linker amino acid sequence(s) -L- will typically be short (*e.g.* 20 or fewer amino acids *i.e.* 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples comprise short peptide sequences which facilitate cloning, poly-glycine linkers (*i.e.* comprising  $\text{Gly}_n$  where  $n = 2, 3, 4, 5, 6, 7, 8, 9, 10$  or more), and histidine tags (*i.e.*  $\text{His}_n$  where  $n = 3, 4, 5, 6, 7, 8, 9, 10$  or more). Other suitable linker amino acid sequences will be apparent to those skilled in the art. A useful linker is GSGGGG (SEQ ID 1), with the Gly-Ser dipeptide being formed from a *Bam*HI restriction site, thus aiding cloning and manipulation, and the  $(\text{Gly})_4$  tetrapeptide being a typical poly-glycine linker.

-A- is an optional N-terminal amino acid sequence. This will typically be short (e.g. 40 or fewer amino acids i.e. 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples include leader sequences to direct protein trafficking, or short peptide sequences which facilitate cloning or purification (e.g. histidine tags i.e. His<sub>n</sub> where n = 3, 4, 5, 6, 7, 8, 9, 10 or more). Other suitable N-terminal amino acid sequences will be apparent to those skilled in the art. If X<sub>1</sub> lacks its own N-terminus methionine, -A- is preferably an oligopeptide (e.g. with 1, 2, 3, 4, 5, 6, 7 or 8 amino acids) which provides a N-terminus methionine.

-B- is an optional C-terminal amino acid sequence. This will typically be short (e.g. 40 or fewer amino acids i.e. 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples include sequences to direct protein trafficking, short peptide sequences which facilitate cloning or purification (e.g. comprising histidine tags i.e. His<sub>n</sub> where n = 3, 4, 5, 6, 7, 8, 9, 10 or more), or sequences which enhance protein stability. Other suitable C-terminal amino acid sequences will be apparent to those skilled in the art.

15 Most preferably, n is 2 or 3.

### ***The saccharide antigen***

The saccharide antigen is generally the capsular polysaccharide of a GBS or a derivative thereof. Suitable derivatives include oligosaccharide (e.g. from 3 to 150, preferably 8 to 100, monosaccharide units) fragments of the polysaccharide (e.g. refs. 12 to 16), de-acetylated saccharides (Ref. 16), N-acroylated saccharides (16), saccharides with terminal aldehyde groups, etc.

20 The saccharide is preferably conjugated to a carrier molecule to enhance immunogenicity (e.g. see refs. 4 to 23 etc.). In some embodiments of the invention the GBS saccharide is conjugated to a GBS protein as defined above, thereby giving a polypeptide/saccharide combination of the invention in a single molecule. In other embodiments the GBS saccharide is conjugated to a non-GBS protein, in which case the conjugate will be combined with a separate GBS protein to give a polypeptide/saccharide combination of the invention.

25 Non-GBS carrier polypeptides include tetanus toxoid, the *N.meningitidis* outer membrane protein (24), synthetic peptides (25, 26), heat shock proteins (27, 28), pertussis proteins (29, 30), protein D from *H.influenzae* (31), cytokines (32), lymphokines (32), hormones (32), growth factors (32), toxin A or B from *C.difficile* (33), iron-uptake proteins (34) etc. Preferred carrier proteins are the CRM197 diphtheria toxoid (35) and tetanus toxoid.

30 The saccharide and polypeptide are joined covalently. This may involve a direct covalent bond between the saccharide and polypeptide, or indirect coupling via a linker or spacer may be used (e.g. via a B-propionamido linker (16), etc.). Any suitable conjugation chemistry may be used (e.g. reductive amination (21) etc.). Linkage is preferably via a terminal saccharide in the polysaccharide.

A single carrier molecule may carry saccharide antigens of a single type (*e.g.* saccharides derived from a single GBS serotype) or may carry multiple different antigens (*e.g.* saccharides derived from multiple GBS serotypes, all conjugated to the same carrier).

The saccharides can, of course, be prepared by various means (*e.g.* purification of the 5 saccharide from GBS, chemical synthesis, *etc.*), in various sizes (*e.g.* full-length, fragmented, *etc.*) and may be derivatised for linking to carriers. They are preferably prepared in substantially pure form (*i.e.* substantially free from other streptococcal saccharides) or substantially isolated form. Processes for preparing capsular polysaccharides from GBS are well known in the art (*e.g.* refs. 36 to 10 39) and processes for preparing oligosaccharides from polysaccharides are also known (*e.g.* hydrolysis, sonication, enzymatic treatment, treatment with a base followed by nitrosation, *etc.* (12 to 16)).

As an alternative to using a saccharide antigen in non-conjugated combinations, a peptide mimetic of the GBS capsular polysaccharide may be used (*e.g.* 40). Suitable peptides can be selected by techniques such as phage display using protective anti-saccharide antibodies. As a further 15 alternative, an anti-idiotypic antibody may be used instead of a saccharide antigen (*e.g.* ref. 41).

#### ***Prime/boost schedules***

Polypeptide/saccharide combinations of the invention may be given as single doses or as part 20 of a prime/boost schedule. In a prime/boost schedule, the combinations may be used as the priming dose, the boosting dose(s), or both.

If a combination is used for both priming and boosting, it is preferred to use the same combination both times. If a combination is used for only one of priming and boosting, it is preferred that the other dose should use the polypeptide or saccharide on which the combination is based. Thus the invention provides a prime-boost schedule where either (i) one of the saccharide and 25 polypeptide antigens is used for priming an immune response and a combination are used for boosting the response, or (ii) combined saccharide and polypeptide antigens are used for priming an immune response but only one is used for boosting the response.

Various timings for priming and boosting are suitable for use with the invention. In one embodiment, a priming dose is given to a child and a booster is given to a teenager (13-18 years) or 30 young adult (19-25 years). In another embodiment, a priming dose is given to a teenager or young adult and a booster is given during pregnancy. In another embodiment, a priming dose is given to a female who intends to become pregnant and a booster is given during pregnancy.

#### ***Immunogenic pharmaceutical compositions***

35 Polypeptide/saccharide combinations are formulated as immunogenic compositions, and more preferably as compositions suitable for use as a vaccine in humans (*e.g.* children or adults).

Vaccines of the invention may either be prophylactic (*i.e.* to prevent infection) or therapeutic (*i.e.* to treat disease after infection), but will typically be prophylactic. Accordingly, the invention includes a method for the therapeutic or prophylactic treatment of GBS infection in an animal susceptible to GBS infection comprising administering to said animal a therapeutic or prophylactic amount of the immunogenic compositions of the invention.

5 The composition of the invention is preferably sterile.

The composition of the invention is preferably pyrogen-free.

The composition of the invention generally has a pH of between 6.0 and 7.0, more preferably to between 6.3 and 6.9 *e.g.* 6.6 $\pm$ 0.2. The composition is preferably buffered at this pH.

10 Other components suitable for human administration are disclosed in reference 42.

Vaccines of the invention may be administered in conjunction with other immunoregulatory agents. In particular, compositions will usually include an adjuvant. Preferred further adjuvants include, but are not limited to, one or more of the following set forth below:

A. Mineral Containing Compositions

15 Mineral containing compositions suitable for use as adjuvants in the invention include mineral salts, such as aluminium salts and calcium salts. The invention includes mineral salts such as hydroxides (*e.g.* oxyhydroxides), phosphates (*e.g.* hydroxyphosphates, orthophosphates), sulphates, *etc.* {*e.g.* see chapters 8 & 9 of ref. 43}), or mixtures of different mineral compounds, with the compounds taking any suitable form (*e.g.* gel, crystalline, amorphous, *etc.*), and with adsorption being preferred. The mineral containing compositions may also be formulated as a particle of metal salt. See ref. 44.

B. Oil-Emulsions

25 Oil-emulsion compositions suitable for use as adjuvants in the invention include squalene-water emulsions, such as MF59 (5% Squalene, 0.5% Tween 80, and 0.5% Span 85, formulated into submicron particles using a microfluidizer). See ref. 45.

Complete Freund's adjuvant (CFA) and incomplete Freund's adjuvant (IFA) may also be used as adjuvants in the invention.

C. Saponin Formulations

30 Saponin formulations, may also be used as adjuvants in the invention. Saponins are a heterologous group of sterol glycosides and triterpenoid glycosides that are found in the bark, leaves, stems, roots and even flowers of a wide range of plant species. Saponin from the bark of the *Quillaia saponaria* Molina tree have been widely studied as adjuvants. Saponin can also be commercially obtained from *Smilax ornata* (sarsaparilla), *Gypsophilla paniculata* (brides veil), and *Saponaria officianalis* (soap root). Saponin adjuvant formulations include purified formulations, such as QS21, 35 as well as lipid formulations, such as ISCOMs.

Saponin compositions have been purified using High Performance Thin Layer Chromatography (HP-LC) and Reversed Phase High Performance Liquid Chromatography (RP-

HPLC). Specific purified fractions using these techniques have been identified, including QS7, QS17, QS18, QS21, QH-A, QH-B and QH-C. Preferably, the saponin is QS21. A method of production of QS21 is disclosed in U.S. Patent No. 5,057,540. Saponin formulations may also comprise a sterol, such as cholesterol (see WO 96/33739).

5 Combinations of saponins and cholesterols can be used to form unique particles called Immunostimulating Complexes (ISCOMs). ISCOMs typically also include a phospholipid such as phosphatidylethanolamine or phosphatidylcholine. Any known saponin can be used in ISCOMs. Preferably, the ISCOM includes one or more of Quil A, QHA and QHC. ISCOMs are further described in EP 0 109 942, WO 96/11711 and WO 96/33739. Optionally, the ISCOMS may be  
10 devoid of additional detergent. See ref. 46.

A review of the development of saponin based adjuvants can be found at ref. 47.

C. Virosomes and Virus Like Particles (VLPs)

15 Virosomes and Virus Like Particles (VLPs) can also be used as adjuvants in the invention. These structures generally contain one or more proteins from a virus optionally combined or formulated with a phospholipid. They are generally non-pathogenic, non-replicating and generally do not contain any of the native viral genome. The viral proteins may be recombinantly produced or isolated from whole viruses. These viral proteins suitable for use in virosomes or VLPs include proteins derived from influenza virus (such as HA or NA), Hepatitis B virus (such as core or capsid proteins), Hepatitis E virus, measles virus, Sindbis virus, Rotavirus, Foot-and-Mouth Disease virus,  
20 Retrovirus, Norwalk virus, human Papilloma virus, HIV, RNA-phages, Q $\beta$ -phage (such as coat proteins), GA-phage, fr-phage, AP205 phage, and Ty (such as retrotransposon Ty protein p1). VLPs are discussed further in WO 03/024480, WO 03/024481, and Refs. 48, 49, 50 and 51. Virosomes are discussed further in, for example, Ref. 52

D. Bacterial or Microbial Derivatives

25 Adjuvants suitable for use in the invention include bacterial or microbial derivatives such as:

(1) *Non-toxic derivatives of enterobacterial lipopolysaccharide (LPS)*

Such derivatives include Monophosphoryl lipid A (MPL) and 3-O-deacylated MPL (3dMPL). 3dMPL is a mixture of 3 De-O-acylated monophosphoryl lipid A with 4, 5 or 6 acylated chains. A preferred "small particle" form of 3 De-O-acylated monophosphoryl lipid A is disclosed in  
30 EP 0 689 454. Such "small particles" of 3dMPL are small enough to be sterile filtered through a 0.22 micron membrane (see EP 0 689 454). Other non-toxic LPS derivatives include monophosphoryl lipid A mimics, such as aminoalkyl glucosaminide phosphate derivatives e.g. RC-529. See Ref. 53.

(2) *Lipid A Derivatives*

35 Lipid A derivatives include derivatives of lipid A from *Escherichia coli* such as OM-174. OM-174 is described for example in Ref. 54 and 55.

(3) *Immunostimulatory oligonucleotides*

5 Immunostimulatory oligonucleotides suitable for use as adjuvants in the invention include nucleotide sequences containing a CpG motif (a sequence containing an unmethylated cytosine followed by guanosine and linked by a phosphate bond). Bacterial double stranded RNA or oligonucleotides containing palindromic or poly(dG) sequences have also been shown to be immunostimulatory.

10 The CpG's can include nucleotide modifications/analogs such as phosphorothioate modifications and can be double-stranded or single-stranded. Optionally, the guanosine may be replaced with an analog such as 2'-deoxy-7-deazaguanosine. See ref. 56, WO 02/26757 and WO 99/62923 for examples of possible analog substitutions. The adjuvant effect of CpG oligonucleotides 15 is further discussed in Refs. 57, 58, WO 98/40100, U.S. Patent No. 6,207,646, U.S. Patent No. 6,239,116, and U.S. Patent No. 6,429,199.

15 The CpG sequence may be directed to TLR9, such as the motif GTCGTT or TTGCGT. See ref. 59. The CpG sequence may be specific for inducing a Th1 immune response, such as a CpG-A ODN, or it may be more specific for inducing a B cell response, such a CpG-B ODN. CpG-A and CpG-B ODNs are discussed in refs. 60, 61 and WO 01/95935. Preferably, the CpG is a CpG-A ODN. 20 Preferably, the CpG oligonucleotide is constructed so that the 5' end is accessible for receptor recognition. Optionally, two CpG oligonucleotide sequences may be attached at their 3' ends to form "immunomers". See, for example, refs. 62, 63, 64 and WO 03/035836.

(4) *ADP-ribosylating toxins and detoxified derivatives thereof.*

20 Bacterial ADP-ribosylating toxins and detoxified derivatives thereof may be used as adjuvants in the invention. Preferably, the protein is derived from *E. coli* (i.e., *E. coli* heat labile enterotoxin ("LT"), cholera ("CT"), or pertussis ("PT"). The use of detoxified ADP-ribosylating toxins as mucosal adjuvants is described in WO 95/17211 and as parenteral adjuvants in WO 25 98/42375. Preferably, the adjuvant is a detoxified LT mutant such as LT-K63, LT-R72, and LTR192G. The use of ADP-ribosylating toxins and detoxified derivatives thereof, particularly LT-K63 and LT-R72, as adjuvants can be found in Refs. 65, 66, 67, 68, 69, 70, 71 and 72 each of which 30 is specifically incorporated by reference herein in their entirety. Numerical reference for amino acid substitutions is preferably based on the alignments of the A and B subunits of ADP-ribosylating toxins set forth in Domenighini et al., Mol. Microbiol (1995) 15(6):1165 – 1167, specifically incorporated herein by reference in its entirety.

E. Human Immunomodulators

Human immunomodulators suitable for use as adjuvants in the invention include cytokines, such as interleukins (e.g. IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-12, etc.), interferons (e.g. interferon- $\gamma$ ), macrophage colony stimulating factor, and tumor necrosis factor.

35 F. Bioadhesives and Mucoadhesives

Bioadhesives and mucoadhesives may also be used as adjuvants in the invention. Suitable bioadhesives include esterified hyaluronic acid microspheres (Ref. 73) or mucoadhesives such as

cross-linked derivatives of poly(acrylic acid), polyvinyl alcohol, polyvinyl pyrrolidone, polysaccharides and carboxymethylcellulose. Chitosan and derivatives thereof may also be used as adjuvants in the invention. E.g., ref. 74.

G. Microparticles

5 Microparticles may also be used as adjuvants in the invention. Microparticles (*i.e.* a particle of ~100nm to ~150 $\mu$ m in diameter, more preferably ~200nm to ~30 $\mu$ m in diameter, and most preferably ~500nm to ~10 $\mu$ m in diameter) formed from materials that are biodegradable and non-toxic (*e.g.* a poly( $\alpha$ -hydroxy acid), a polyhydroxybutyric acid, a polyorthoester, a polyanhydride, a polycaprolactone, *etc.*), with poly(lactide-co-glycolide) are preferred, optionally treated to have a 10 negatively-charged surface (*e.g.* with SDS) or a positively-charged surface (*e.g.* with a cationic detergent, such as CTAB).

H. Liposomes

Examples of liposome formulations suitable for use as adjuvants are described in U.S. Patent No. 6,090,406, U.S. Patent No. 5,916,588, and EP 0 626 169.

15 I. Polyoxyethylene ether and Polyoxyethylene Ester Formulations

Adjuvants suitable for use in the invention include polyoxyethylene ethers and polyoxyethylene esters. Ref. 75. Such formulations further include polyoxyethylene sorbitan ester surfactants in combination with an octoxynol (Ref. 76) as well as polyoxyethylene alkyl ethers or ester surfactants in combination with at least one additional non-ionic surfactant such as an octoxynol (Ref. 77).

Preferred polyoxyethylene ethers are selected from the following group: polyoxyethylene-9-lauryl ether (laureth 9), polyoxyethylene-9-stearyl ether, polyoxyethylene-8-stearyl ether, polyoxyethylene-4-lauryl ether, polyoxyethylene-35-lauryl ether, and polyoxyethylene-23-lauryl ether.

J. Polyphosphazene (PCPP)

25 PCPP formulations are described, for example, in Ref. 78 and 79.

K. Muramyl peptides

Examples of muramyl peptides suitable for use as adjuvants in the invention include N-acetyl-muramyl-L-threonyl-D-isoglutamine (thr-MDP), N-acetyl-normuramyl-L-alanyl-D-isoglutamine (nor-MDP), and N-acetylmuramyl-L-alanyl-D-isoglutaminyl-L-alanine-2-(1'-2'-dipalmitoyl-*sn*-glycero-3-hydroxyphosphoryloxy)-ethylamine MTP-PE).

L. Imidazoquinolone Compounds.

Examples of imidazoquinolone compounds suitable for use as adjuvants in the invention include Imiquamod and its homologues, described further in Ref. 80 and 81.

The invention may also comprise combinations of aspects of one or more of the adjuvants identified above. For example, the following adjuvant compositions may be used in the invention:

(1) a saponin and an oil-in-water emulsion (ref. 82);

- (2) a saponin (e.g., QS21) + a non-toxic LPS derivative (e.g., 3dMPL) (see WO 94/00153);
- (3) a saponin (e.g., QS21) + a non-toxic LPS derivative (e.g., 3dMPL) + a cholesterol;
- (4) a saponin (e.g. QS21) + 3dMPL + IL-12 (optionally + a sterol) (Ref. 83);

5 combinations of 3dMPL with, for example, QS21 and/or oil-in-water emulsions (Ref. 84);

- (5) SAF, containing 10% Squalane, 0.4% Tween 80, 5% pluronic-block polymer L121, and thr-MDP, either microfluidized into a submicron emulsion or vortexed to generate a larger particle size emulsion.
- (6) Ribi<sup>TM</sup> adjuvant system (RAS), (Ribi Immunochem) containing 2% Squalene, 0.2% Tween 80, and one or more bacterial cell wall components from the group consisting of monophosphoryl lipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), preferably MPL + CWS (Detox<sup>TM</sup>); and
- (7) one or more mineral salts (such as an aluminum salt) + a non-toxic derivative of LPS (such as 3dPML).

15 Aluminium salts and MF59 are preferred adjuvants for parenteral immunisation. Mutant bacterial toxins are preferred mucosal adjuvants.

The composition may include an antibiotic.

GBS polypeptide(s) and saccharide(s) in the compositions of the invention will be present in 'immunologically effective amounts' *i.e.* the administration of that amount to an individual, either in 20 a single dose or as part of a series, is effective for treatment or prevention of disease. This amount varies depending upon the health and physical condition of the individual to be treated, age, the taxonomic group of individual to be treated (*e.g.* non-human primate, primate, *etc.*), the capacity of the individual's immune system to synthesise antibodies, the degree of protection desired, the formulation of the vaccine, the treating doctor's assessment of the medical situation, and other 25 relevant factors. It is expected that the amount will fall in a relatively broad range that can be determined through routine trials.

Typically, the compositions of the invention are prepared as injectables. Direct delivery of the compositions will generally be parenteral (*e.g.* by injection, either subcutaneously, intraperitoneally, intravenously or intramuscularly or delivered to the interstitial space of a tissue) or 30 mucosal (*e.g.* oral or intranasal [85,86]). The compositions can also be administered into a lesion. The invention provides a syringe containing a composition of the invention.

Once formulated, the compositions of the invention can be administered directly to the subject. The subjects to be treated can be animals; in particular, human subjects can be treated. The vaccines are particularly useful for vaccinating children and teenagers, and more particularly 35 females.

As well as GBS polypeptides and saccahrideres, the composition of the invention may comprise further antigens. For example, the composition may comprise one or more of the following further antigens:

- antigens from *Helicobacter pylori* such as CagA [87 to 90], VacA [91, 92], NAP [93, 94, 95], HopX [e.g. 96], HopY [e.g. 96] and/or urease.
- 5 – a saccharide antigen from *N.meningitidis* serogroup A, C, W135 and/or Y, such as the oligosaccharide disclosed in ref. 97 from serogroup C [see also ref. 98] or the oligosaccharides of ref. 99.
- a saccharide antigen from *Streptococcus pneumoniae* [e.g. 100, 101, 102].
- 10 – an antigen from hepatitis A virus, such as inactivated virus [e.g. 103, 104].
- an antigen from hepatitis B virus, such as the surface and/or core antigens [e.g. 104, 105].
- an antigen from *Bordetella pertussis*, such as pertussis holotoxin (PT) and filamentous haemagglutinin (FHA) from *B.pertussis*, optionally also in combination with pertactin and/or agglutinogens 2 and 3 [e.g. refs. 106 & 107].
- 15 – a diphtheria antigen, such as a diphtheria toxoid [e.g. chapter 3 of ref. 108] e.g. the CRM<sub>197</sub> mutant [e.g. 109].
- a tetanus antigen, such as a tetanus toxoid [e.g. chapter 4 of ref. 128].
- a saccharide antigen from *Haemophilus influenzae* B [e.g. 98].
- an antigen from hepatitis C virus [e.g. 110].
- 20 – an antigen from *N.gonorrhoeae* [e.g. 111, 112, 113, 114].
- an antigen from *Chlamydia pneumoniae* [e.g. refs. 115 to 121].
- an antigen from *Chlamydia trachomatis* [e.g. 122].
- an antigen from *Porphyromonas gingivalis* [e.g. 123].
- polio antigen(s) [e.g. 124, 125] such as OPV or, preferably, IPV.
- 25 – rabies antigen(s) [e.g. 126] such as lyophilised inactivated virus [e.g. 127, RabAvert<sup>TM</sup>].
- measles, mumps and/or rubella antigens [e.g. chapters 9, 10 & 11 of ref. 128].
- influenza antigen(s) [e.g. chapter 19 of ref. 128], such as the haemagglutinin and/or neuraminidase surface proteins.
- an antigen from *Moraxella catarrhalis* [e.g. 129].
- 30 – an antigen from *Streptococcus pyogenes* (group A streptococcus) [e.g. 3, 130, 131].
- an antigen from *Staphylococcus aureus* [e.g. 132].
- an antigen from *Bacillus anthracis* [e.g. 133, 134, 135].
- an antigen from a virus in the flaviviridae family (genus flavivirus), such as from yellow fever virus, Japanese encephalitis virus, four serotypes of Dengue viruses, tick-borne encephalitis virus, West Nile virus.

- a pestivirus antigen, such as from classical porcine fever virus, bovine viral diarrhoea virus, and/or border disease virus.
- a parvovirus antigen *e.g.* from parvovirus B19.
- a prion protein (*e.g.* the CJD prion protein)
- 5 – an amyloid protein, such as a beta peptide [136]
- a cancer antigen, such as those listed in Table 1 of ref. 137 or in tables 3 & 4 of ref. 138.

The composition may comprise one or more of these further antigens.

Toxic protein antigens may be detoxified where necessary (*e.g.* detoxification of pertussis toxin by chemical and/or genetic means [107]).

10 Where a diphtheria antigen is included in the composition it is preferred also to include tetanus antigen and pertussis antigens. Similarly, where a tetanus antigen is included it is preferred also to include diphtheria and pertussis antigens. Similarly, where a pertussis antigen is included it is preferred also to include diphtheria and tetanus antigens. DTP combinations are thus preferred. Saccharide antigens are preferably in the form of conjugates. Carrier proteins for the conjugates are  
15 the same as those described above for GBS saccharide conjugation, with CRM197 being preferred.

Antigens in the composition will typically be present at a concentration of at least 1 $\mu$ g/ml each. In general, the concentration of any given antigen will be sufficient to elicit an immune response against that antigen.

20 As an alternative to using protein antigens in the composition of the invention, nucleic acid encoding the antigen may be used. Protein components of the compositions of the invention may thus be replaced by nucleic acid (*preferably* DNA *e.g.* in the form of a plasmid) that encodes the protein.

#### *Methods of treating patients*

25 The invention provides polypeptide/saccharide combinations of the invention for use as medicaments. The medicament is preferably able to raise an immune response in a mammal (*i.e.* it is an immunogenic composition) and is more preferably a vaccine.

30 The invention also provides a method of raising an immune response in a patient, comprising administering to a patient a composition of the invention. The immune response is preferably protective against streptococcal disease, and may comprise a humoral immune response and/or a cellular immune response.

The invention also provides the use of polypeptide/saccharide combination of the invention in the manufacture of a medicament for raising an immune response in a patient. The medicament is preferably an immunogenic composition (*e.g.* a vaccine). The medicament is preferably for the prevention and/or treatment of a disease caused by GBS (*e.g.* meningitis, sepsis, chorioamnionitis).

The invention also provides for a kit comprising a first component comprising the immunogenic compositions of the invention. The kit may further include a second component comprising one or more of the following: instructions, syringe or other delivery device, adjuvant, or pharmaceutically acceptable formulating solution.

5 The invention also provides a delivery device pre-filled with the immunogenic compositions of the invention.

10 The invention also provides a method for raising an immune response in a mammal comprising the step of administering an effective amount of a composition of the invention. The immune response is preferably protective and preferably involves antibodies and/or cell-mediated immunity. The method may raise a booster response.

#### *Process for manufacturing*

The invention provides a process for preparing a composition of the invention, comprising the step of mixing (i) one or more GBS polypeptide antigens with (ii) one or more GBS saccharide antigens.

15 The process may comprise the step of covalently linking the GBS polypeptide to the GBS saccharide in order to form a conjugate.

#### *Definitions*

The term "comprising" means "including" as well as "consisting" e.g. a composition "comprising" X may consist exclusively of X or may include something additional e.g. X + Y.

20 The term "about" in relation to a numerical value  $x$  means, for example,  $x \pm 10\%$ .

The word "substantially" does not exclude "completely" e.g. a composition which is "substantially free" from Y may be completely free from Y. Where necessary, the word "substantially" may be omitted from the definition of the invention.

#### **MODES FOR CARRYING OUT THE INVENTION**

25 GBS serotype III is grown in Todd-Hewitt broth as described in reference 36 and its capsular polysaccharide was purified. The polysaccharide is depolymerised, sized and purified as described in reference 14 to give oligosaccharide antigen. Similar procedures are used to prepare capsular polysaccharides from other GBS serotypes.

30 The oligosaccharide is either admixed with or covalently conjugated (directly or via a linker) to purified serotype V protein. Preferably, the protein comprises a GBS antigen or a fragment thereof selected from the group consisting of GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691.

It will be understood that the invention has been described by way of example only and modifications may be made whilst remaining within the scope and spirit of the invention. All documents cited herein are incorporated by reference in their entirety.

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**CLAIMS:**

1. An immunogenic composition comprising a GBS saccharide antigen and at least two GBS polypeptide antigens, wherein said GBS saccharide antigen comprises a saccharide selected from GBS serotype Ia, Ib, and III, and wherein said GBS polypeptide antigens comprise a combination of at least two polypeptide or fragments thereof selected from the antigen group consisting of GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691.
2. The immunogenic composition of claim 1, wherein said GBS polypeptide antigens further comprise a GBS polypeptide or a fragment thereof of serogroup II.
3. The immunogenic composition of claim 1, wherein said GBS polypeptide antigen combination comprises GBS 80 or a fragment thereof.
4. The immunogenic composition of claim 3, wherein said GBS polypeptide antigens comprise a combination of two GBS antigens or fragments thereof selected from the group consisting of (1) GBS 80 and GBS 91, (2) GBS 80 and GBS 104, (3) GBS 80 and GBS 147, (4) GBS 80 and GBS 173, (5) GBS 80 and GBS 276, (6) GBS 80 and GBS 305, (7) GBS 80 and GBS 313, (8) GBS 80 and GBS 322, (9) GBS 80 and GBS 328, (10) GBS 80 and GBS 330, (11) GBS 80 and GBS 338, (12) GBS 80 and GBS 358, (13) GBS 80 and GBS 361, (14) GBS 80 and GBS 404, (14) GBS 80 and GBS 404, (15) GBS 80 and GBS 656, (16) GBS 80 and GBS 690, and (17) GBS 80 and GBS 691.
5. The immunogenic composition of claim 4, wherein said combination is selected from the group consisting of (1) GBS 80 and GBS 338; (2) GBS 80 and GBS 361, (3) GBS 80 and GBS 305, (4) GBS 80 and GBS 328, (5) GBS 80 and GBS 690, (6) GBS 80 and GBS 691 and (7) GBS 80 and GBS 147.

6. The immunogenic composition of claim 4, wherein said combination comprises GBS 80 and GBS 691.
7. The immunogenic composition of claim 1, wherein said composition comprises a combination of at least three GBS polypeptide antigens.
8. The immunogenic composition of claim 7, wherein said combination comprises GBS 80 and GBS 691.
9. The immunogenic composition of claim 7, wherein said combination comprises GBS 80.
10. The immunogenic composition of claim 1, wherein at least one GBS polypeptide antigen is covalently linked to the GBS saccharide antigen.
11. The immunogenic composition of claim 1, wherein said GBS saccharide antigen is covalently linked to a carrier protein.
12. The immunogenic composition of claim 11, wherein said carrier protein is selected from the group consisting of tetanus toxoid, diphtheria toxoid, *N. meningitidis* outer membrane protein, heat shock protein, pertusis protein, protein D from *H. influenzae*, and toxin A or B from *C. difficile*.
13. The immunogenic composition of claim 12, wherein said carrier protein is selected from the group consisting of tetanus toxoid and diphtheria toxoid.
14. The immunogenic composition of claim 13, wherein said carrier protein is a diphtheria toxoid.
15. The immunogenic composition of claim 14, wherein said diphtheria toxoid is CRM197.

16. A method for the therapeutic or prophylactic treatment of GBS infection in an animal susceptible to GBS infection comprising administering to said animal a therapeutic or prophylactic amount of the immunogenic composition of claim 1.
17. A method for the manufacture of a medicament for raising an immune response against GBS comprising combining a GBS saccharide antigen and at least two GBS polypeptide antigens, wherein said GBS saccharide antigen comprises a saccharide selected from GBS serotype Ia, Ib, and III, and wherein said GBS polypeptide antigens comprise a combination of at least two polypeptide or fragments thereof selected from the antigen group consisting of GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691.

## SEQUENCE LISTING

SEQ ID NO. 1

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SEQ ID NO. 3

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SEQ ID NO. 5

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## SEQ ID NO. 8

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**SEQ ID NO. 10**

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SEQ ID NO. 11

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ATTGATGCTGGTTTTGATAAAAATCATGAGCGTGGCCCTTAACAGAACAAAACCTAACAGCTTACCAATCAAAGGAAATCTTGTAAAAGCTAAA  
AAAGAGCACGGTATTACCTATGGCGAGTGGGTCAATGATAAGGTTGCTTATTACACGACTATAGTAAAGAGTGGTAAACGCTGTTGATCAAGAA  
CACGGCACACACGTGTCAGGGATCTGTCAAGGAAATGCTCATCTGAAATGAAAGAACCTTACCGCTAGAAGGTCGATGCCCTGAGGCTCAATTG  
CTTTTGATGCGTGTGCAAAATTGTAATGGACTAGCAGACTATGCTGCTAACAGCTATCAGAGATGCTGTCACCTGGGAGCTAACGTC  
ATTAAATATGAGCTTTGGTAATGCTGCACTAGCTAACCCCAACTTCCAGACGAAACAAAAGCCTTGTGATGCTAACATCAAAGGTTGAGC  
ATTGTCACCTCAGCTGTAATGATAGCTTGGGGCAAGGCCCCGCTCACCTCTAGCAGATCATCTGATTAATGGGTGGCTGGACACCTGCA  
CGCGCAGATTCAACATTGACAGTTGCTTACAGCCCAGATAAACAGCTACTGAAACTGCTACGGTCAAAACAGACGATCATCAAGATAAGAA  
ATGCCCTGTATTTCAACAAACCGTTTGAGCCAACAAGGCTACGACTATGCTTATGCTAACATGCTGTAACGAAAGAGGATGATTTAAGGATGTC  
GAAGGTAAGATTGCCCTATTGAGACGTGGCGATATTGATTTCAAAAGATAAGATTGCTAACAGCTAAAAAGCTGGTCTGTAAGGGCTCTGATCTT  
GACAATCAAGACAAGGCCCTCCCGATTGAAATTGCCAAATGTTGACAGATGCCCTGGGCTTATCTAGTCAAGAGACGCTCTTATTAAAAGAC  
ATACCCCCAAAACCAATTCTTCACTGCAACCTAACGTTGACAGCTAACGCTAACGAGCTTCTGCTGGGCTCTGACA  
GCTGACGGCAATATTAAACCGGATATTGAGCACCCGCCAACGATATTGTCATCAGTGGCTAACACAAGTATGCCAAACTTCTGGAACCTAGT  
ATGTCGACCATTGGTAGCGGGTATCATGGACTGTTGCAAAGCAATATGAGACACAGTATCCTGATATGACACCATCAGCGCTCTGATTTA  
GCTAAGGAAAGTATTGATGAGCTCAGCAACTGCCATTATGATGAGATAAGGTTTCTCTCGCAACAGGGAGCAGGAGCAGTGGAT  
GCTAAAAAAAGCTTACAGCAGCAACGATGTTGACAGATAAGGACAATACCTAACGCAAGGTTTACCTGAAATGTTCTGATAAAATTGAGTA  
ACAGTAAACAGTTCAACAAATCTGATAAACTCTAACAGGTTTACCTAACGAGATGCTAACAGATAAGGTTTACCTGCAACGAGCTTCTGCTT  
GCTCTAAAGCATTGATGAGACATCATGGCAAAACATCCAGCCAATAGCAGAACAGTCACCGTCTTCAATCGATGCTAGTCGATT  
AGCAAGGACTTGCTTGGCCAAATGAAAATGGCTATTTCTTAGAAGGTTTGTGTTGTTCAAAAGATCCTACAAAAGAAGAGCTTAFGAGCATT  
CCATATATTGGTTTCCGAGGTGATTGGCAATTGTCAGCCCTAGAAAACCAATCTATGATGAGCAAGACGGTAGCAGCTACTATCATGAGCA  
AATAGTGTGCAACAGGACAATTAGATGTTGATGATTACAGTTTACGCTCTGAAAAAAACTTACAGCACTTACACAGAGCTAACCCATGG  
ACGATTATTAAGCTGCAAGAAGGGTTGAAAACATAGAGGATATCGATATTCTCAGAGATCACAGAACACCATTGCAAGGTTTACCTT  
CAAGAGCATGATGCCACTACTATATCCACCGTCACGCTAACGGCAACCATATGCTGCGATCTCTCCAAATGGGAGCGTAAACAGAGATTATGTC  
CAATTCCAAGGACTTTCTGCGTAATGCTAAAACCTGTGGCTGAAGTCTTGGACAAAGAAGGAAATGGTTGTTGACAAGTGAGGTAACCGAG  
CAAGTTGTTAAAACCTAACAACTGACTTGGCAAGCACCTGGTTCAACCCGTTGGGAGCGTAAAGATAAAAGCAGGCCAAA  
GTTGTTGCTAACCGAACCTACACCTATGTTGCTACACGGCAGTAGCTCAGGTCACAGGCAAAAGAACACACTGATTGATGTTGAGC  
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CTGAGCGTATTGCTTACACTTATGAGTGGAGATCTGCCAACACAGAGTATTTCTCCAAATGAAGAGTGGTACCTTACTCTTCTGAGAG  
GCTGAAACATGGAAGGGCTACTGTTCCATTGAAAATGTCAGACTTTACTTATGTTGTTGAGAGATATGGCTGGTAAACATCACTTACACCAAGT  
ACTAAGCTATTGGAGGCCACTCTAATAAGCCAGAACAGACGGTTCAGATCAAGCACCAGAACAGAACCCAGAACAGAACAGAACCGGT  
TCAGGTCACACACCGAGATAAAAAGGAAACTAACCGAGAAAAGAGATAGTTCAAGGTCACACCCAGGTTAAACTCCTCAAAAGGTCATCTCT  
CTGACTCTAACAGAACCGGACTTCTAACGGCTTCTAGTCAACAAAGCATCAACAGAGATCAGTTACCAACGACTAATGACAAGGATACAAATCGT  
TTACATCTCTTAAAGTTAGTTGACCACTTTCTTCTGGGA

**SEO ID NO. 12**

MRKKQKLPFDKLALIALISTSILLNAQSDIKANTVTEDETPATEQAVEPPQPIAVSEESRSSKETKTSQTPSDVGETVADDANDLAPQ  
APAKTADTPATSKATIRDLNDPSHVKTLOQEKGKAGTVVAVIDAGFDKNHEAWRLTDKTKARYQSKENLEKAKKEHITYGEWVN  
DKVAYYHDYSKDGKNAVDQEHGHTHVGILSGNAPSEMKEPYRLEGAMPEAQLLMRVEIVGLADYARNYAQAIRDADVNLGAKVIN  
MSFGNAALAYANLPDETKKAFDYAKSKGVSIUTSAGNDSSFGGKPRPLADHPDYGVVGTAAADSTLTVASYSPDKQLTETATVK  
TDDHQDKEMPVISTNRFEPNKAYDYAYANRGTKEDDFKDVEGKIALIERGDIDFKDKIANAKKAGAVGVLIYDNQDKGFPIELPNV  
DQMPPAIFISSRDGLLLKDNPPTITFNATPKVLTASGKLSRFSSWGLTADGNIKPDIAAPGQDILSVANNKYAKLSGTSMSAP  
LVAGIMGLLQKQYETQYPDMTPSERLDLAKKVLMLSSATALYDEDEKAYFSPROQGAGAVDAKKASAATMYVTDKDNTSSKVHLNNV  
SDKFEVTVTVHNKSDKPQELEYQYQTVQTDKVDGKHFA LAPKALYETSWOKITIPANSSKVTVPIDASRFSKDLLAQMKNGYFLEG  
FVRFKQDPTKEELMSIPIYIGFRGDFGNLSALEKPIYDSKDGSYYHEANSDAKQLDGDGLQFYALKNNFTALTTESNPWTI KAV  
KEGVENIEDIESSETETIFAGTFAKQDDDSHYIYIHRHANGPKYAISPNGDGNRDYVQFQGTFLRNNAKLNVAEVLDEGNVWTS  
EVTEQVVKNYNNDLASTLGSTRFEKTRWDGKDGDGVVANGTYTVRVRYTFISGKAEQHTDFDVIDNTTPEVATSATFSTEDSR  
LTLASKPKTSQPVYRERIAYTMDLEDLPTTEYISPNEDEGTFTLPEEAETMEGATVPLKMSDFTYVVEDMAGNITYTPVTKLLEGHS  
NKPEQDGSDQAPDKKPKAEPQDGSGQTDPKKKETKPEKDSSGQTPGKTPQKGQSSRTLEKRSSKRALATKA STRDQLPTNDKDT  
NRLHLLKLVMTTEFLG

**SEQ ID NO. 13**

ATGGGACGAGTAATGAAAACAATAACAAACATTGAAAATAAAAAGTTTAGTCCTGGTTAGCACGATCTGGAGAAGCTGCTGC  
ACGTTGTTAGCTAAGTAGGAGCAATAGTGCAGTTAATGATGGCAACCATTGATGAAAATCCAACAGCACAGTCTTGTGG  
AAGAGGGTATTAAAGTGGTTGTGGTAGTCATCCTTAGAATTGTTAGATGAGGATTTGTACATGATTAACCCAGGAATA  
CCTTATAACAATCCTATGGTCAAAAAGCATTAGAAAACAAATCCCTGGTAGCTGACTGAAGTGGAAATTAGCATACTTAGTTCAGA  
ATCTCAGCTAATAGGTATTACAGGCTCAACGGAAAACGACAACAGCATGATTGAGAAGCTTAAAGATACTCTAGTTATGGAATT  
GAGGTTGTTAGCTGGGAATATCGCTTCTGCTAGTGAAAGTGTGAGGCTGAGATGATAAGAGATACTCTAGTTATGGAATT  
TCAAGTTTCAGCTAATGGAGTTAGGAATTTCGCTCTATATTGAGTAATTACTAATTAAATGCCAACTCATTAGATTATCA  
TGGGTCTTCTAGAGATTATGTTGCTGCAAAATGGAATATCCAAAATCAAATGTCCTCATCTGATTTTGGTACTTAATTAAATC  
AAGGTATTCTAAAGAGTTAGCTAAAACACTAAAGCAACAATGTCCTTCTACTACGGAAAAGTTGATGGTCTTACGTA  
CAAGACAAGCAACTTTCTATAAAGGGGAGAATATTATGTCAGTAGATGACATTGGTCTCCAGGAAGCCATAACGTAGAGAATGC  
TCTAGCAACTATTGCGTTGCTAAACTGGCTGTATCAGTAATCAAGTTATTAGAGAACTTTAAGCAATTGGAGGTGTTAAC  
ACCGCTTGCATCACTCGTAAGGTTATGGTATTAGTTCTATAACGACAGCAAGTCAACTAATATATTGGCAACTAAAAAGCA  
TTATCTGGCTTGTATAACTAAAGTTATCCCTAATTGCAAGGAGGTCTGATCGCGGTAAATGAGTTGATGAAATTGATACCGATAT  
CACTGGACTAAACATATGGTGTAGGGAGAATCGGCATCTGAGTAAACGCTGCTGCACAAAAGCAGGAGTAACCTATAGCG  
ATGCTTGTAGATGTTAGAGATGCGGTACATAAGCTTATGAGGTGGCACAACAGGGCAGTGTATCTGCTAAGTCCTGCAAATGCA  
TCATGGGACATGTATAAGAATTGCAAGTCCGTGGTGTAGAATTGATACTTTCGAAAGTCTTAGAGGAGAG

**SEQ ID NO. 14**

MGRVMKTIITFENKKVLVGLARSGEAAARLLAKLGAIVTVNDGKPFDENPTAQSLLEEGIKVVCGSHPLELLEDIFCYMIKNPGI  
PYNNPMVKKALEKQIPVLTEVELAYLVSESQLIGITGSNGKTTTTMIAEVLNAGGQRLLAGNIGFPASEVVQAANDKDTLVMEL  
SSFQLMGVKEFRPHIAVITNLMPHLDYHGSFEDYVAKWNIQNMSSDFLVLNFNQGISKELAKTTKATIVPFSTTEKVDGAYV  
QDKQLFYKGGENIMSVDDIGVPGSHNVENALATIAVAKLAGISNOVIRETLSNFGVKHRLQSLGKVGHSFYNDSKSTNILATQKA  
LSGFDNTKVILIAGGLDRGNEFDELIPIITGLKHMVVLGESASRVKRAAQKAGVTYSDALDVRDAVHKAYEVAQQGDVILLSPANA  
SWDMYKNFVEVRGDEFIDTFESLRGE

**SEQ ID NO. 15**

ATGAAACGTTAGCTGTTTAACTAGGGTGGTACGCCCTGGTATGAAACGCTGCTATCCGTGCAAGTTGTTGCAAAGCAATTCTGAAAGGTATG  
GAAGTTACGGCATCAACCAAGGTTACTATGGTATGGTACAGGGGATATTCCCTTGGATGCTAATTCTGTTGGGATACTATCAACCGTGG  
GGAACGTTTACGTTACGTTACGTTACCTGAATTGCTGAACTGAGCACGGTTCCAGCTTGGTATTGCGGGTACATTGATAAC  
GTACTAGTTACGGTGGTATGGTTCTATCATGGCTATGCGCTAACTGAGCACGGTTCCAGCTTGGTATTGCGGGTACATTGATAAC  
GATATCGTTGGCAGTACTAATTTGTTGAGGTTGAGGAAATGAGGAGATATCGCTCTTGTGAGGATCTTGCACGGCTTGGTATTGCGGGTACATTGATAAC  
AACCGTACTTTGTTGAGGTTGAGGAAATGAGGAGATATCGCTCTTGTGAGGAGATATCGCTCTTGTGAGGATCTTGCACGGCTTGGTATTGCGGGTACATTGATAAC  
GAAGAAGAGTCATATTGATGAACTTGTCTAAATGTTAGAGCTGGCTATGAGCTGGTAAACATCACCAAAATCATCGCTCTTGCAGAAGGTGTT  
ATGAGTGGTGTAGGAGTTGCAAAAACAATGAAAGCAGCAGGAGACGATAGCGATCTCGTGTGACGAATTAGGACATCTGCTCCGGTGGTATTGCGGGTACCTGCTCCAC  
ACCGAGGAGTGGTGTAGGAGTTGCACTCGTGTGAGCTGGTCAATTGTTGAAAGAAGGTTGCTTGTGACTGATGAAAGGAAAATCGTTGTTAAATACCG  
CATAAAGCGGACCTCGCTGGCAGCACTTAATGTCACCTGCAACCAAAGTAGTAAA

**SEQ ID NO. 16**

MKRIVALTSGDAPGMNAIRAVRKAISEGMEVYGINQGYGMVTGDIPLDANSVGDINRGGTFLRSARYPEFAELEGQLKGIEQLKKHGIEG  
VVVIGGDSYHGAMRLTEHGPAPVGLPPTIDNDIVGTDYTFGDTAVATAVENLDRLRDTASHNRFTVUEVMGRNAGDIALWSGIAAGQDIIIVP  
EEEFNIDEVVSNSVRAGYAAKGHHQITIVLAEGVMSGDEFAKTMKAAGDDSDLRVTNLGHLLRGGSPTARDRVLASRMGAYAVQLKEGRGGLAVGVH  
NEEMVESPIGLAEEGALFSLTDEGKIVVNNPHKADLRLAALNRDLANQSSK

**SEQ ID NO. 17**

ATGAATAAAAAGGTACTATTGACATCGACAATGGCAGCTTCGCTATTATCAGTCGCAAGTGTCAAGCACAAGAAACAGATACTGACGGACAGCA  
CGTACTGTTACAGGGTAAAGGCTGATTGGTAAAGCAAGACAATAATCATCATATACTGTGAAATATGGTGTACACTAAGCGTTATTCAGAA  
GCAATGTCATATTGATGAACTGCTTACGAAATAACATGCAAGATACTAATCTTATTTATCTGAGGACAACACTGACAGTAACCTACGAT  
CAGAAGAGTCATATGCCACTTCAATGAAAATAGAAACACAGCAACAAATGCTGCTGGTCAACAAACAGCTACTGTTGAGTTGAAAACATCAA  
GTTCTGTTGCAAGACAAAAGTTCTCTCAATACAATTCGAGGGTATGACACAGGAGACGCAACAAACAGGTTGTTGCAATGAAAGACATAT  
TCTTCTGCGCAGCTTGAATCAAAGAAGTATTGACACAAGAGCAAGCTGTTACTCAAGCAGCAGCTAATGAAACAGGTTACCAACAGCTCCGTG  
AAGTCGATTACTTCAGAAGTCCAGCAGCTAAAGAGGAAGTAAACCAACTCAGACGTCAGTCAGTCAGTCAACAAACAGTATCACAGCTTGTGTT  
GCCCTGAAACACCGAGCTCCAGTAGCTAAAGTAGCACCCGGTAGAGACTGTAGCAGGCCCTAGAGTGGCAAGTGTAAAGTAGTCACCTCTAAAGTA  
GAAACTGGTGTGATCACCGAGAGCATGTATCAGCTCCAGCTGGTAGCTACGACTTCACAGCTACAGACAGTAAGTTACAAGCAGACTGAGTT  
AAGAGCCTCCGGTAGCACAAGCTCCAAACAGCAACACCCGGTAGCACACCCGGTAGCTACAGCTACAGGTTACAACAAACAAATGCA  
GGGCTCCAACCTCATGTTGCAAGCTTATAAAGAAAAGTAGCGTCACATTATGGAGTTAATGAAATTGAGTACATCACCGTGGGGAGATCCAGGTGAT  
CATGGTAAAGGTTAGCAGTTGACTTAATCAAGCACTTGTGAAATAAAGTTGCAAGTACTCTACACAAATATGGCAGCAAAT  
AACATTTCATATGTTATCTGGCAACAAAGTTTACTCAAATACAAACAGTATTGACTGGACTGCTAATACTTGGAAATGCAATGCCAGATCGTGGT  
.GGCGTTACTGCCAACCAACTATGACCACGTTACGTATCTTAAACAAATAATAAAAAGGAAGCTTGGCTTCTTTTATATGCCCTGAAAT  
AGACTTCAAGGTTCTTATAATAATTGTTATA

**SEQ ID NO. 18**

MNKKVLLTSTMAASLLSVASVQAQETDTTWARTVSEVKADLVQDNKSSYTVKYGDTLSVISEAMSIDMNVLAKINNIADINLIYPETTLTVTYD  
QKSHTATSMKIELTPATNAAGQTATVDLKTQNQSVADQKVSINTISEGTMPEAATTIVSPMKTYSAPALKSKEVLAQEQAQSQAANEQVSPAPV  
KSITSEVPAAKEEVKPTQTSVQSQTIVSPASVAEPTPAPVAKVAPVRTVAAPRVASVKVUTPKVETGASPEHVSAPAVPVTTSPATDSKLQATEV  
KSVPVQAQKAPTATPVAQPASTTNAVAAHPENAGLQPHVAAKYEKVASTGVNEFSTYRAGDPGHDHGKGLAVDFIVGTONQALGNKVAQYSTQDMAAN  
NISYIWQOKFYSNTNSIYGPANTWNAMPDRGGVTANHYDHVHSFNK

SEQ ID NO. 19

ATGAAAAAGAAAATTATTTGAAAGTAGTGTCTTGTTAGTCGCTGGACTTCTATTATGTTCTAAGCGTGTCCGGGACCAAGTCGGTGTCAAGTTATAGCGTCAATGACTTCTATGGTGCACTTGACAATACTGGAACAGCAAATATGCCCTGATGAAAAGTTGCTAATGCTGGTACTGCTGCTCAATTAGATGCTTATGGTGACGCTCAAAAAGATTTCAAAACAAACTAACCTCAATGCTGAAAGCATTAGGGTTCAAGCAGGGCATATGGTTGGA GCAAGTCGGCAGCAACTCTGGGCTTCAAGATGAAACCAACTGTCAAAATTTAATGCAATGATTTGAGTATGGCACATTGGTAAACCATGAAATTTGATGAGGGTTGGCAGAATATACTGTTATCGTTAAGGCCCCTGCTCAGATCTAATATAATATTACCAAACTCATACCCACATGAAAGCTGCAAAACAAGAAAATTGTTAGTGGCAAATGTTATTGATAAAGTTAACAAACAATTCTTACAATTGGAAGCCATTACGCTATTAAAAAATATT CCTGAAATAACAAAAGTGTGAACGTTGGCTTATCGGGATTGTACCAGAACATCCAAACCTGCTTACGTTAAAATTATGAAACAATATGAA TTTTAGATGAAAGCTGAAACATGTTAAACACGCCAAAGAATTACAAGCTAAAATGCTAAAGCTATTGTTAGTTCTGCACATGTAACCGAACAGTAAAAAAATGATATTGTAAGGTGAAGCAGCAGAAAATGATGAAAAAAAGTCAATCAACTCTTCCCTGAAAATAGCGTAGATATTGTTCTGGTGTGGA CACAATCATCAATATAACAAATGTTCTGGTAAAACCTGTTAGTCAACAGCCTCTCAAGGAAAAGCCTATGCTGATCTGGTGTCTTA GATACTGATACACAAGATTCTATGGACCCCCCTTCAGCTTAAAGTAATTGCAAGTTGCTCTGGTAAAACAGGTTAGTGCCTGATATTCAAGCCTT GTGACCAAGCTAATACTATCGTTAAACAAGTAACAGAACGCTAAAATTGGTACTGCGCAGGTAAGTGTCACTGATTACCGCTTCTGATCAAGAT AATGTTAGTCCGGTAGGCAGCTCATCACAGAGGCTCAACTAGCAATTGCTGAAAAAGCTGGCAGATATGCAATTGCTGATCAAGATGGT GGCATTCTGTGCTGACTTACTCATCAACACCAGATGGAAACATCACCTGGGAGCTGCACAAAGCAGTTCAACCTTTGGTAAATCTTCAAGTCGTC GAAAATTACTGGTAGAGATCTTATAAAGCACTCAACGAAACATACGACCAAAACAAAATTCTCTTCAAAATAGCTGGTCTGGATACACTTAC ACAGATAATAAAGAGGGCGGGGAGAAAACACCATTTAAAGTTGTTAAAGCTTATAAATCAATGGTGAGGAAATCAATTCTGATGCAAAATAACAAA TTAGTTATCAATGACTTTTATTCGGTGGTGTAGGGCTTGCAGAAATGCCAAACTCTAGGAGCCATTACCCCGATACAGAGGTA TTATGGCTTATATCACTGATTAGAAAAGCTGGTAAAAGTGGCTCCAAATAAAACCTAAAATCTATGTCACTATGAAAGATGGTTAAT GAAACTTACACAAAATGATGGTACACATAGCATTATAAGGAAACTTATTGTTAGATGCAAGGAAATATTGTAAGCACAAGAGATTGTTACAGAC ACTTTAAACCAAAACAAAATCACAAAAATCAACCCCTGTAACTACAACTTCAACAAAACAAATTACACCAATTACAGCTATTACCCCTATG AGAAAATTGGCAAACCATCAACACTGTTAGTAAACCAAAACAAATTACACCAATTACAGCTATTACCCCTATGTTAGGTTAAT GGGTGTGGACTTATAGGAATTGCTTAAATACAAAGAAAAACATATGAA

SEQ ID NO. 20

MKKKIIILKSSVLGVAGTSIMFSSVFDQVGVQVIGVNDFHGALDNTGTANMPDGKVNAGTAAQLDAYMDDAQKDFKQTNPNGESIRVQAGDMVG  
ASPANSGLLQDDEPTVKNFNAMNEYGTLGNHEFDEGLAEYNRIVTGKAPAPDSNINNITKSYPHEAAKQEIVVANVIDKVNQI PYNWKPYAIKNI  
PVNNKSVNVGFFIGIVTKDIPNLVLRKNYEQYEFLEAETIVKYAKELQAKNVKAIVVLAHPATSKNDIAEGEAAEMMKVNQLFPENSVDIVFAG  
HHHQYTNGLVGKTRIVQALSQGKAYADVRGVLDLTDQDFIETPSAKVIAVAPGKKTGSADIQAIVDQANTIVKQVTEAKIGTAEVSMITRSVDQD  
NVSPVGSLLITEAQALIARKSWPDIDFAMTNNGGIRADLLIKPDGTITWGAAQAVQPGFMNILQVVEITGRDLYKALNEQYDQKONFFLQIAGLRYTY  
TNKEGGEPETFPKVVKAYKSNGEEINPDAKYKLVINDFLFGGGDGFASFRNAKLLGAINPDTEVF MAYITDLEKAGKKVSVPNKP KIYVTMCMVN  
ETITQONDGTHSI I KKLYDLRGNIVAQEIVSDTILNQTKSKSTKINPVTTIHKKQLHQFTAIPMRN YGKPSNSTTVSKSQLPKTNSEYGQSFLMSV  
FGVGLIGIALNTKKKHMK

SEQ ID NO. 21

ATGAATAAACCGCGTAAATCCTGCAACACTTGGTCCCTGCAGGTGAAATTCCGGTGGTAAGAAGTTGGTGAAGTCGGATACTGGGGTGAAGC  
CTTGACGTAGAACCTCAGCAGAAAAAATTGCTCAATTGATAAAAGAAGGTGCTAACGTTTCCGTTCAACTTCTCACATGGAGATCATGCTGAG  
CAAGGAGCTCGTATGGCTACTGTTCTGAAAGCAGAAGGATTGCAAGGACAAAAGTTCGCTTCCCTGTAACCTAAAGGACCTGAAATTGCTAC  
GAACATTTTGAAAGATGGTGCAGATTCCATTCTACAAACAGGTACAAATTACATGTTGCTACTAAGCAAGGTATCAAATCAACTCCAGAAGTC  
ATTGCTATTGAAATGTTGCTGGTGGACTTGCACATCTTGTGACTGAGCTTGAAGGTTGTAACGAAATTCTTGTGATGTTGTAACATTAGGTCCTTACTGT  
TTTGCAAAAGATAAAGACACTCGTAATTGAAAGTAGTTGTTGAGAATGATGCCATTGGTAAACAAAAAGGTGTAACACATCCCTTACTA  
ATTCCCTTCCAGCAGCTTGCAAGCAGCATAATGCTGATATCCGTTTGAGCAAGGACTTAACCTTATTGCTATCTCATTGTAACGTACT  
GCTAAAGATGTTAATGAAGTCTGCTATTGTAAGGAAACTGGSMATGGACACGTTAAGTTGTTGCTAAATTGAAATCAACAGGTATCGAT  
AATATTGATGAGATTATCGAAGCAGCAGATGGTATTATGATTGCTGCTGGTGTATGGGATTCGAAGTTCCATTGAAATGGTTCCAGGTTACCAA  
AAAAATGATCATTTACTAAAGTTAATGCGACTGGTAAAGCAGTTATTACAGCAACAAATTGCTTGTAAACAAATGACTGATAAACACCGTCGACTCGT  
TCAGAAGTATCTGATGTTCAATGCTGTTATTGATGCTACTGATGCTACAAATGCTTTCAGGTGAGTCAGCTAACGTTAAACACCAGTTGAGTC  
GTTCTGACATGGCTACTATTGATAAAATGCTAAACATTACTCAATGAGTATGGTCGCTTAGACTCATCTGCATTCCCACGTAATAACAAA  
GATGTTATTGCTGATCTGGGTTAAAGATGCAACACACTCAATGGATATCAAACATTGTTGTAACAATTACTGAAACAGGTAAACAGCTCGTGCATT  
TCTAAATTCTGGTCCAGATGCGACAGATTTGGCTTACATTGTTGAAAGGTTGCAACGTTCTATTGATGATTAACATTGTTGTTATCCCTGTC  
CGAGACAAACAGCAGCATCACAGATGATATTGTTGAGGGTCTGAGACCTGTAACACTGAAACAGGATTGTTGAACTCAGGGCATAATATCGTTATC  
GTTGCAAGGTGTTCTGAGCTACAGGTGAACTAACACAAATGCGTGTGTTGACTGTTAA

**SEQ ID NO. 22**

MNKRVKIVATLGPAVEFRRGKKFGESGYWGESLDVEASAECIAQLIKEGANVFRNFHGDHAEQGARMATVRKAEEIAGQKVGFLLDTKGPETR  
ELFEDGADFHYSYTTGKLRVATKOGIKSTPVEIALNVAAGGLDIFDDVEVGKOILVDDGKLGLTVFAKDKDTRFEVVVENDGLIGKOKGVNIPYTK

I PFPALAEADNADIRFGLEQGLNFIAISFVRTAKDVNEVRAICEETGXGHVKLFAKIENQQGIDNIDEIIEAADGIMIARGDMGIEVPFEMPVYQ  
KMIITKVNAAGKAVITATNMLETMTDKPRATRSEVDVFNAVIDGTATMLSGESANGKYVESVRTMATIDKNAQTLNEYGRLDSSAFPRNNKT  
DVIASAVKDATHSMDIKLWVTTETGTNTARAISKFRPDADILAVTFDEKVQRSLMINWGVIPVLADKPASTDDMFEVAERVALEAGFVESGDNIVI  
VAGVPVGTGGTNTMRVRTVK

**SEQ ID NO. 23**

TTGTCTGCTATAATAGACAAAAGGTGGTATTTATGTATTTAGCATTAATCGGTGATATCATTAACTCAAAACAGATACTTGA  
ACGTGAAACTTCCAACAGCTTTCAAGCTTACAGCAACTATGACCGAATCTGATGTATGGTGAAGAGCTGATTTCTCCATTCACTA  
TTACAGCTGGTGATGAATTCAAGCTTATTGAAACCATTAAAAAGGTATTCAAATTATTGACCATATTCAACTAGCTCTAAA  
CCTGTTAATGTAAGGTCGGCCTCGGTACAGAACATTATAACATCCATCAATTCAAATGAAAGTATCGGTGCTGATGGTCTGC  
CTACTGGCATGCTCGCTCAGCTATTAACTATACATGATAAAAGTATTGAAACAGTCAGTAGCTATTGCCCTGATGATG  
AAGACACAAAACCTGAGATTAAACACTAAATGTCATTICAGCTGGTGATTTATCAAGTCAAATGGAACAGTCAGTAGCTATTGCCCTGATGATG  
ATGCTTGACACTTAACACTCAAGATAATTATCAAGAACAAATTCAACATCAAAGTAGCCCACTGAAAATATTGAACCTAG  
TGCCTGACTAAACGCCCTAAAGCAAGCGGTCTGAAGATTACTTAAGAACGAGAACACAGGCAGCCGATCTATTAGTTAAAAGGT  
GCACACTAAACACTAAAGGGGAAGCTATGATTTC

**SEQ ID NO. 24**

MSAIIDKKVVIIFMYLALIGDIINSKQILERETFQQSFFQQLMTELSDVYGEELISPFTITAGDEFQALLKPSKKVQIIDHIQLALKPVNVRFLGLTG  
NIITSINSNESIGADGPAYWHARSAINHIDKNDYGTQVAICLDDEDQNLELTNSLISAGDFIKSKWTTNFQMLEHLILQDNYQEKFQHQKLAQ  
LENIEPSALTKLKASGLKIYLRTRTQADLLVKSTQTKGGSYDF

**SEQ ID NO. 25**

ATGTTTTATAACAATTGAAGAGCTGGTAGAGCAAGCTAATAGCCAACATAAGGTAACATAGCAGAGCTCATGATCCAAACGGAAATTGAAATGACT  
GGTAGAAGCTGTGAAGAAATTCTGTTATTATGTCTCCGAAATCTTGAAGTCTGAAAGCTCTGTTATTGATGATTAAACCCCTAGTAAATCACT  
AGTGGTTAACAGCGGGTGTGCTGCAAGATGGATCAATTAACTTACAATCAGAAAAAACTATTCAAGATACCAACTCTAGCTGCCGTTAGGAAT  
GCTATGGCTTAATGAGTTAACAGCTTAACTGAGTGGACTGGTCTGCAACACCAACTGCAAGGTAGTGCAGGATGTTACCAAGCTGTGATTTCTACA  
GCCATTGAAAAGCTTAATTAAACAGAAGAGCAACTTGATTTCTATTAACTGCAAGGCGCATTGGTCTCGTCAATTGTAATAATGCCCTTATC  
TCAGGTGCAAGAGGAGGTGCAAGCTGAAGTTGGTCAGCTAGTGTATGGCTGCGGCTGTTAGTTATGGCTGCTGGAGGTACTCCCTTCAA  
GCTAGCCAACCTATAGCATTGTTAAAGATGCTTGGACTTATCTGTGACCCCTGTCAGGTTAGTTGAAGTCCCTGTTAGTGAAGCAGGGAAAT  
GCTCTGGATCAAGTTGCACCTGTTGCTGATATGCCCTGGCTGTATTGAATCGCAAATTCCAGTAGATGAAGTTATTGATGCAATGTAT  
CAAGTTGGATCAAGTTACCGACTGCTTCTGAGACTGCAAGAGGAGACTGCTGCCACCGCACAGGAAGACGTTAGTAAAGAAATTGTT  
GGGAA

**SEQ ID NO. 26**

MFYTIIEELVEQANSQHKGNIAELMIQTEIEMTGRSREEIRYIMSRNLEVMKASVIDGLPSKSISGLTGDAVKMDQYLOSGKTISDTTILAVERN  
AMAVNELNAKMLGLVCATPTAGSAGCLPAVISTAEKLNLTTEEQLDFLFTAGAFGLVIGNNASISGAEGGCQAEVGSASAMAAAALVMAAGGTPQ  
ASQIAAFVIKMLGLICDPVAGLVEVPCVKRNALGSSFALVAADMALAGIESQIPVDEVIDAMYQVGSSLPTAFRETAEGGLAATPTGRRRYSKEIF  
GE

**SEQ ID NO. 27**

ATGAGCGTATATGTTAGTGGAAATGGAATTATTCCTTGGAAAGAAATTATAGCGACCATAAACAGCATCTCTCGACTTAAAGAAGGAATT  
CTAAACATTATATAAAAATCAGACTCTATTAGAATCTTACAGGAAGCATAACTAGTGAACCCAGGGTCTGAGCAATACAAAGATGAGAC  
ACGTAAATTAAATTGCTTTACCGCTTGAAGAGGCTCTGCTTCAAGGTGTTAATTAAAGCTTATCATAATTGCTGTGTTAGGG  
ACCTCACTTGGGGAAAGAGTGTGCTGCAAAATGCTTGTATCAATTGAAAGAAGGAGAGCGTCAAGTAGATGCTAGTTATTAGAAAAGCATCTG  
TTTACCATATTGCTGATGAATTGATGCTTATCATGATATTGTTGGAGCTTGTATGTTATTCAACCGCTGTCTGCAAGTAATAATGCCGTAAT  
ATTAGGAACATAATTACTCAAGATGGCATTGTGATTAGCTTTGTGGGGCTGTGATGAGTTAAGTGTATTCTTCTGAGGCTTACACATCA  
CTAGGAGCTTAAATACAGAAATGGCATGTCAGCCCCTATTCTTGGGAAAGAATCAATTGGGGCTGGCTGGTTTGTGTTCTGTCAAAG  
ATCAGTCTTACGTTAAATGGAAAATTATGGCTTCTTATTACTTCAAGATGGTTATCATATAACAGCACCTAACGCAACAGGTGAAGGGCGC  
ACAGATTGCAACAGCAGCTAGTGAACGAGGTATTGACTACAGTGAAGATTGACTATATTACAGGTACCGTACGGTACAGGTACTCAAGTAATGATAAA  
ATGGAAAAAAATATGTATGGTAAGTTTCCGACAACGACATTGATCAGCAGTACCAAGGGCAACGGGTACACTCTAGGGGCTGCAGGTATTA  
TCGAATTGATTAAATTGTTAGCGGAACAGAGGAACAGACACTGTAACAGCAACTAAAGGATGGGAGTACAAGCTTCCAGAAAATTGCTA  
TCATCAAAAGAGGAAATACCAAAATAAGGAATGCTTAAATTTCGTTGGGAAATAATAGTGGTCTTATTGTCATCTTGTGATT  
CCTCTGAAACATTACCTGCTAGGAGAAAATCTTAAAGGCTATCTTACATCTGTTCTGCTTCTGCTAATGAAATGACTTCTATAACCCATAG  
AAAAGTTGCTAGTAATTCAACGACTTGAAGCATTACGCTTAAAGGGCTAGACCACCCAAAATGCAACCCAGCACAAATTAGAAAATGGA  
TGATTTCACAAATGGTGGCGTAACACAGCTCAAGCACTAATAGAAAGCAATATTCTAAAGAATACTTCAAAGTAGGAAATTGTA  
TTTACAACACTTCTGGACCAGTTGAGGTTGTTGAAGGTTATTGAAAAGCAAATCACAACAGAAGGATATGCAACATGTTCTGCTTACGGCTT  
TTACAGTAATGCAAGCAGCTGGTATGCTTCTATCATTCTTAAATAACAGGTCTTCTATCTGTCATTCTGACAAATAGTGGAGCGCTTGATGG  
TATACAATATGCAAGGAATGATGCGTAACGATAATCTAGACTATGTGATTCTGTTCTGCTAATCAGTGGACAGACATGAGTTTATTGTTG  
CAACAATTAAACTATGATAGTCAAAATGTTGCTGGTCTGATTATTGTTCAAGCACAAGTCTCTCTCGTCAAGCATTGGATAATTCTCTATAATAT  
TAGGTAGTAAACAATTAAAGATAGCCATAAAACATTACAGATGTGACTATTGTTGATGCTGCGCTTCAAATTATTACAGACTTAGGACT  
AACCATAAAAGATATCAAAGGTTGTTGGAATGAGCGGAAGAAGGCAGTTAGTTCAAGATTATGATTCTTAGCGAACTTGTCTGAGTATTATAAT  
ATGCCAAACCTTGTCTGGTCAAGTTGATTTCATCTAATGTTGCTGGTGAAGAAGTGGACTATACTGTTAATGAAAGTATAGAAAAGGCTATT  
ATTAGTCCTATCTTATTGATCTTCTGGTGTATCTCTTGTCTATTGAAAAAGG

**SEQ ID NO. 28**

MSVYVSGIGISSLGKNYSEHKQHFLKEGISKHLYKNHDSILESYTGSITSDPPEVPEQYKDETRNFKFAFTAFEEALASSGVNLKAYHNIAVCLG  
TSLGGKSAGQNALYQFEEGERQVDASLLEKASVYHIADELMAYHDIVGASYVI STACSASNNAVILGTONLDQGDCCDAICGGCDELSDISLAGFTS  
LGAINTEMACQPYSSGKGINLGEAGAGFVVLVKDQSIAKYGIIGGLITSDGYHTATPKPTGEGAAQIAKQLVTQAGIDSEIDYINGHGTQANDK  
MEKNMYGKFPTTLLISSTKGQTGHTLGAAGIIELINCLAAIEEOTVPATKNEIGIEGFPENFVYHQKREYPIRNALNFSFAFGNNNSGVLLSSLDS  
PLETLPLARENLKMAILSSVASISKNESLSITYEKVASNFDFEALRFKGARPKTVNPQAQRKMDDFSKMVAVTTAQALIESNINLKKQDTSKVGVIV  
FTTLSGPVEVVEGIEKQITTEGYAHVSASFPTVMNAAGMLSIIIFKITGPLSVISTNSGALDGIQYAKEMMRNDNLDYVILVSANQWTDMSFMWW  
QQLNYDSQMFVGSDYCSAQVLSRQALDNPPIILGSKQLKYSHKTVDVMTIFDAALQNLSSLGLTIKDIKGFVWNERKAVSSDYDFLANLSEYYN  
MPNLASQGQFSSNGAGEELDYTMESIEKGYYLVLSYSIFGGISFAIIIEKR

**SEQ ID NO. 29**

ATGAAAATAGATGACCTAAGAAAAGCACAATGTTGAAGATCGCGCTCCAGTAGCGGAGGTTCAATTCTCTAGCGGAGGAAGTGGATTACCGATT  
CTTCACACTTTATTGCTGCGAGGGAGTTGGAAAACCAAGCTTGTTTAATCATCTTACTGCTACTTGGCGAGGGAGCTAACAGCATTTT  
ATGACTCATCCTCACCTCTAGTACCACTCTCAGAATGCTCAGCTTGTTGATAATAGCGCAACGAGAGAACAAATCGATTTCGTTAATAAA  
GTCTCCTGCCTCAACTGAGGATTCTGCTACAAGAATTCACAAACCAAGGTTTGGAAATTATAAGGAACAAAATCTGTTTACACCAATTCA  
ATTCAAACAGGTTGGTATAGGTGAATCTGCTCAGGACCATTTTATTGTTAGCAGAGATAAAAAAATCTATCTTGTATTTCTTACAAATGAA  
TTATCACATAATATGGTCTACTGGTATTTGCTATGGCTACGTCATGCCACGAAGTTGGTACACACATTCAAACAGAGTTAGGATTATG  
GATAAGTATAATAGAATGCGACAGGACTACTAAGAAAGCAGAAATGCTTAAATGTCGGCTAGAACCTTAAAGCAGATTATTATGCAAGGGTA  
TGGGCTCACTACATCAGGGAAAAATCTTCTAGAACAAAGGAGACTTGAAGAGGCCATGAATGCTGCCACGCCCTCGGAGACGATACCCCTCAG  
AAAGAAACCTACGGAAAAATTAGTGCCTGATAGCTTACCCATGGAACAGCTGAACAACGCCAACGTTGGTTAACAAAGGTTCAATATGGTAC  
ATCCAACACGGTGTACTTTCTCCGTAGAACATCTA

**SEQ ID NO. 30**

MKIDDLRKSDNVEDRRSSSGSFSSGGSGLPILQLLLRGSWKTKLVLITILLLGGGLTSIFNDSSSPSYQSQNVRSVDNSATREQIDFVNK  
VLGSEDFWSQEFQTOGFGNYKEPKLVLVYTNISIQTGCGIGESASGPFYCSADKKIYLIDISFYNELSHKYGATGDFAMAYVIAHEVGHIIQTELGIM  
DKYNRMRHGLTKKEANLVRLELQADYYAGVWAHYIRGKNLLEQGDFEEAMNAAHAVGDDTLQKETYGKLVPDFTHGTAEQQRWFNKGQFYGD  
IQHGDTFSVHL

**SEQ ID NO. 31**

ATGAAAAGATTACATAAAACTGTTATAACCGTAATTGCTACATTAGGTATGTTGGGGTAATGACCTTGGCTTCCAACGCAGCCGAAACCGTA  
ACGCCGATAGTACATGCTGATGTCATTCTGATACGAGCCAGGAATTCTAAAATAATTAAATGCTATTGGTAACCTACCAATTCAA  
TATGTTAATGTTATTATGAAATTAAATAATCAGACAATTAAATGCTGATGTCATTGTTAAAGCTATGTTAAAGCTTAAATGACAAATTGAAACCA  
CAAAGACTATCAACTGCTAATGCAATGCTTGTAGAAGCATTCTCAATATCAAATCGCAGAGATAACCACTCTCCGATGCAAATTGAAACCA  
TTAGGTTGGCATCAAGTAGCTACTAATGACCATTGACATGCTGACAAGGGCATTAAATTGCTATGCTTGTGAACTGAAATTGAAACAGGTT  
TGGGATGCTTCCGTGTCAAATCCTAAATGTTGTCACACAAACAGCTCATTCCAACCAATCAAATCAAATGTCGGACAAAATTATTAT  
GAAAGCTTAACTTCGTAAGCGGTTGACCAAAACAAACGTTGTTACCGTGTAACTCCATTGTAACGTAATGACTGATTTAGTTCCATTGCA  
ATGCACCTAGAACGCTAAATCACAAGATGCCACATTAGAACATTAAATGTCATTCCAAACACACAAGCATCATACACTATGATTATGCAACAGGA  
GAAATAACACTAAAT

**SEQ ID NO. 32**

MKRLHKLFITVIATLGMLGVMTFGLPTQPQNVTPIVHADVNSVDTSQEFQNNLKNAINLPLFQYVNGIYELNNNQTNLNADVNVKAYVQNTIDNQ  
QLRSLANMIDRTIRQYQNRDITLQDANWKPLGWHQVATNDHYHAVIDKGHLIAYALACMFKGWDASVSNPQNVVQTQAHNSNQSNQKINRGONYY  
ESLVRKAVDQNKRVRYRVTPLYRNDTDLPFAMHLEAKSQDGTLEFNVAIPNTQASYMDYATGEITLN

**SEQ ID NO. 33**

ATGAGTAAACGACAAAATTAGGAATTAGTAAAAAAGGAGCAATTATATCAGGGCTCTCAGTGGCACTAATTGTAATAGGTGGTTTATGG  
GTACAATCTAACCTAATAAGAGTGCACTAAAACACTAACAAAGTTTAATGTTAGAGAAGGAAGTGTCTCGCTCAACTCTTGTGACAGGA  
AAAGCTAACGCTAACAAAGAACAGTATGCTATTGATGCTAACAAAGGTAAATCGAGCAACTGTCACAGTTAAAGTGGGTGATAAAATCACAGCT  
GTCAGCAGTTAGTCAATGATGACACACTGCAACAGCAGCTACGACACTGCTAATGCTAACATTAAATAAAAGTAGCAGCGTCAGATTAAAT  
CTAAAGACACAGGAAGTCTCCAGCTATGGAATCAAGTGAATCTTCTCATCACAAAGGACAAGGGACTAACGACTAGTGGTCCGAC  
AATCGTCTACAGCAAATTATCAAAGTCAAGTCAATGCTTACACAACCAACTCAAGATTGTAATGATGCTTATGAGATGCAACAGGCGAA  
GTAAATAAAGCACAAAAGCATTGAATGACTGTTATTCAAAGTGAAGCTACAGGGACAGTTGTAAGGTTAAATGTAATTGATCCAGCTTCA  
AAAACAGTCAAGTACTTGTCCATGTAGCAACTGAAGGTAACCTCAAGTACAAGGAACGATGAGTGTAGTATTGCTTAATGTTAAAAGAC  
CAGGCTGTTAAATCAAAGGCTATCTGACAAAGGAAGGAAAGTAAATTCTCAATATCTCAAAATTATCAGGTTAACAGGTTTACCGTATCA  
AATGACTCTAATAACGGCTCTAGTGTGCTGAAATTATAAAGTAGATATTACTAGCCCTCTCGATGCAATTAAACAAGGTTTACCGTATCA  
GTTGAAGTAGTTAATGGAGATAAGCACCTTATTGTCCTACAAGTTCTGTGATAAACAAAGATAATAAACACTTTGTTGGGTATACAATGATTCT  
AATCGTAAAATTCTCAAAGTGAAGTCAAATTGGTAAAGCTGATGCTAACAGACACAAGAAATTATCAGGTTTGAAGCAGGACAAATCGTGGT  
ACTAATCCAAGTAAAACCTCAAGGATGGCAAAAATTGATAATATTGATAATCAATGATCTAACCTAATAAGAAATCAGAGGTGAAA

**SEQ ID NO. 34**

MSKRQNLGISSKGAIISGLSVALIVVIGFLWVQSQPNKSAVKTNYKVFNRREGSVSSSTLLTGAKANQEYVYFDANKGNRATVTVKVGDKITAGQLVQYDTTTAQAAAYDTAQNRLNKVARQINNLKITGSLPAMESSDQSSSSQGQGTQSTSGATNRLOQNYQSQANASYNQQLQDLNDAYADAQAEVNKAQKALNDTVITSVSDVGTVEVNSDIDPASKTSQVLHVATEGKLQVQGTMSEYDLANVKKDQAVKIKSKVYPDKEWEKGKISYISNYPEAEANNDSNGSSAVNYKYKVDTSPDALKQGFTVSVEVVNGDKHLIVPTSSVINKDNKHFWVYNDSNRKISKVEVKIGKADAKTQEILSGLKAGQIVVTNPSKTFKDQKIDNIESIDLNSNKKSEVK

**SEQ ID NO. 35**

ATGAAAAAAAATGGAAATTATTGTCCTCACACTACTGACCTCTTTGGTATCTGGCGAACAAAACAACAACTAAACAAGAACACTAAACAAACTATTCTCTAAATGCCTTACACCTATTATGGAAAATCTCTGAAACATCCGAAAAAAAGTAATTAAATTCTTACATATTCTTACACTGGTATTATGTTAAACACTAGGTGTTAATGTTCAAGTTACAGTTAGACTTGAAGAAAGATAGCCCGTTGGTAAACACTGAAAGAAGCTAAACAACTGCAACTGCTGATGATAACAGCTATTGCCGACAAAACCTGATTTAATCATGGTTTCGATCAAGATCCAACATCAATACTCTGAAACAAATGGCACAACCTTAGTTATTAAATATGGTCACAAAATTATTTAGATATGATGCCAGCTGGGGAAAGTATTGGTAAAGAAAAGAAGCTAATCAGTGGGTTAGCAATGGCAATGGAAAACTCTCGCTGTCAAAAAAGATTACACCATACTTAAAGCTAAACACTATTACTATTATGGATTCTTATGATAAAATATCTTATGTTAATGTTGACCGCGGAGAAACTAATCTGATTCAGTTACTGGTTATGCTGCCCGAGAAAAGTCAAAAAGATGTCTTAAAGGGTGGTTACCGTTTCGCAAGAAGCAATCGGTGATTACGGTGGATTATGCCCTGGTAAATATAACAAAACAGCTAAACAAAGCTTACGACGTGTTTATTCCTGACCCCTCATCTTAAAGGCTATCAAAGAAAATACAAT

**SEQ ID NO. 36**

MKKIGIIVLTLTFLVSCGQQTKQESTKTTISKMPKIEGFTYYGKIPENPKVINFNTSYTGYLLKLGVNVSYSLDLEKDSPVF  
GKQLKEAKKLTADDTEAIAAQKPDLIMVFDQDPNINTLKKIAPLTVIKYGAQNYLDMMMPALGVFGKEKEANQWVSQWKTKTAVK  
KDLHHILKPNTTFTIMDFYDKNIYLYCENNFRGGELIYDSLGYAAPEVKKDVFKKGWFTVSQEAIGDYVGDYALVNINKTTKAA  
SSLKESDVWKNLPAVKKHIIIESNYDVFYFSDPLSLEAQLKSFTKAIKENTN

**SEQ ID NO. 37**

ATGAAAGTAAAAAATAGATTAAACGATGGTAGCCTTACTGCTTAACATGTGCTACTTATTCTCATCAATCGTTATGCTGATACAAGTGTAAAGAATACTGACACGAGTGTGACTACGACCTTATCTGAGGAGAAAAGATCAGATGAACTAGACCAGTCTAGTACTGGTTCTCTGAAAATGAATC  
GAGTTCACTCAAGTGAACCAGAAAACAATCCGTCAACTAATCCACCTACAACAGAACCATCGAACCCCTCACCTAGTGAAGAGAACAGCCTGATGGT  
AGAACGAGAACAGAAAATTGGCAATAATAAGGATATTCTAGTGGAAACAAAAGTATTAAATTTCAGAAGATAGTATTAAAGAATTAGTAAAGCAAGTA  
GTGATCAAGAAGAAGTGGATCGCGATGAATCATCATCTTCAAAGCAAATGATGGAAAAAAGGCCACAGTAAGCTAAAAGGAACCTCCCTAAAC  
AGGAGATAGCCACTCAGACTGTAATAGCATCTACGGGAGGGATTATTCTGTTATTAAGTTTACAATAAGAAAATGAAACTTTAT

**SEQ ID NO. 38**

MKVKNKILMVALTVLTCATYSSIGYADTSKNTDTSVVTTLSEEKRSDELDQSSTGSSSENESSSSEPETNPSTNPPTTEPSQPSPEENKPDG  
RTKTEIGNNDIISSTGKVLISEDSIKNFKASSDQEEVDRDESSSSKANDGKKGHSKPKKELPKTDHSHTDVIASTGGIILLSLSFYNKKMKLY

**SEQ ID NO. 39**

ATGAAAAGGATACGGAAAAGCCTTATTTGTTCTGGAGTAGTTACCTTAATTGCTTATGTGCTTGTACTAAACAAAGCCAGAAAAAAATGGCT  
TGTCTAGTAGTGTACTAGCTTTATCCAGTATATTCCATTACAAAAGCAGTTCTGGTGAATTGATATTAAATGATTGATCACAGTCAGGTAT  
TCATGGTTTGACCCCTCATCAAGTGTGTTGCTGCCATTATGATGCTGATCTATTCTTATCATTGGCACACACTAGAAGCTGGCGAGACGT  
TTGGAACCTAGTTGCATCACTCTAAAGTATCTGTAATTGAGCTTCAAAGGTATGACTTTGGATAAGTGTGTTAGGCTTAAAGATGTAGAGGAG  
AAAAGGAGTAGATGAGTCACCTTGTATGACCCCTCACACTTGGAAATGACCCCTGAAAAGTATCTGAGGAAGCACAACATCGCTACACAATTAGC  
TAAAAGGATCCTAAAACGCTAAGGTTATCAAAAGGCTGATCAATTAGTGAACAGGAATGGCTATTGGAGAGAAGTATAAGGAAAATT  
AAAGCTGCAAAAGTCTAAATACTTGTGACTTCACATACGATTCTCATACTTAGCTAAGCAGTACGGGATTGACTCAGTTAGGTATTCAGGGTCT  
CAACCGAGCAAGAACCTAGTGTCTAAAGGCTGAAATCAGGAGTTGTAAGGATAAGACTATTGTTGAAGAAGGAGTCTC  
ACCTAAATTAGCTCAAGCAGTAGCTTCACTCGAGTTAAATTGCAAGTTAAGTCTTARAAGCAGTCCCCAAAACAATAAAAGATTCTTA  
AAAAATTGGAAACTAATCTTAAGGTACTTGTCAAATCGTTAAATCAATAG

**SEQ ID NO. 40**

MKRIRKSLIFVLGVVTLICLCACTKOSQOKNGLSVVTSFVYVSIKAVSGDLNDIKMIRSOSGIHGFEPSVDVAIYDADLFYHSHTLEAWARR  
LEPSLHHSKVSIEASKGMLDKVHGLEDVEAKGVDESTLYDPTHWNPDVKVSEEAQLIATQLAKKDPKNAVKYQKNADQFSKAMIAEKYKPKF  
KAAKSKYFVTSHAFSYLAKRYGLTQLGIAGVSTEQEPSAKKLAETQEFVKTYKVKTIFVEEGVSPKLAQAVASATRVKIASLSPLXAVPKNNKDYL  
ENLETNLKVLVKSLSQ

**SEQ ID NO. 41**

ATGCCTAAGAAGAAAATCAGATACCCCAGAAAAGAAGAGTGTCTTAACGGAATGGCAAAGCGTAACCTGAAATTAAAAACGCAAAGAAG  
ATGAAGAAGAACAAAACGTTAAACGAAAATTACGCTTAGATAAAAAGAAGTAAATTAAATTTCTCTCTGAAAGAACCTCAAATACTACTAA  
ATTAAAGAACCTCATTTCCTAAAGATTCAAGACCTAAGATTGAAAAGAACAGAAAAAGAAAAAGTACTGCAACAGCTTAGCCAAAACAAATCGC  
ATTAGAACTGCACCTATATTGTAGTAGCATTCTAGTCATTAGTTCCGTTCTACTAACCTCTTGTAGTAAGCAAAAACAAATAACAGTTA  
GTGGAATCAGCATAACACTGATGATATTGATAGAGAAAAGCAATATTCAAAAAAGATTATTCTTCTTAAATTAAACATAAAAGCTAT  
TGAACACGTTAGCTGAGAGATGTAGGGTAAAACAGCTCAGATGACTTATCAATTCCCAAATAAGTTCTATCAAGTTCAAGAAAATAAG

ATTATTGCATATGCACATACAAAGCAAGGATATCAACCTGTCTGGAAACTGGAAAAAAGGCTGATCCTGTAATAGTTAGTCAGAGCTACCAAAGCACTTCCTAACATTAACCTTGATAAGGAAGATAGTATTAGCTATTAAAGATTAAAGGCTTAGACCCCTGATTTAATAAGTGAGATTCAAGGTGATAAGTTAGCTGATTCTAAAACGACACCTGACCTCCTGCTGTTAGATATGCACGATGAAATAGTATTAGAATACCATTATCTAAATTAAAGAAAGACTTCCTTTTACAAACAAATTAAAGAAGAACCTTAAGGAACCTCTATTGTTGATATGGAAGTGGAGTTACACAACAAATACCAAGGACAAACAAATAACTCAAATACTAATCAACAAAGGACAACAGATAGCAACAGAGCACCTAACCTCAAAATGTTAAT

**SEQ ID NO. 42**

MPKKKSDTPEKEEVVLTEWQKRNLFLKKRKEDEEEQKRINEKLRLDKRSKLNISSPPEPQNTTKIKKLHFPKISRPKIEKKQQKEKIVNSLAKTNIRTAPIFVVAFLVILVSVFLLTPFSKQKTITVSGNQHTPDDILIEKTNIQKNDYFFSLIFKHKAIEQRLLAEVDVWVKTAQMTYQFPNKFHIQVQBNKIIAYAHTKQGYQPVLETGKADPVNSSELPKHFLTINLDKEDSIKLLIKDLKALDPDLISEIQVISLADSKTTPDLLLDMHDGNSTRPLSKFKERLPFYKQIKKNLKEPSIVDMEVGVTNTIESTPVKAEDTKNKSTDKTQTQNGQVAENSQGQTNNSNQGQQIATEQAPNPQNVN

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WO 2004/041157 A3

(54) Title: GROUP B STREPTOCOCCUS VACCINE

(57) **Abstract:** This application relates to improved Group B Streptococcus ("GBS") saccharide-based vaccines comprising combinations of GBS polysaccharides with polypeptide antigens, and *vice versa*, such that the polypeptide and the saccharide each contribute to the immunological response in a recipient. The combination is particularly advantageous where the saccharide and polypeptide are from different GBS serotypes. The combined antigens may be present as a simple combination where separate saccharide and polypeptide antigens are administered together, or they may be present as a conjugated combination, where the saccharide and polypeptide antigens are covalently linked to each other. Preferably, the immunogenic compositions of the invention comprise a GBS saccharide antigen and at least two GBS polypeptide antigens, wherein said GBS saccharide antigen comprises a saccharide selected from GBS serotype Ia, Ib, and III, and wherein said GBS polypeptide antigens comprise a combination of at least two polypeptide or fragments thereof selected from the antigen group consisting of GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691.

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US03/29167

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : A61K 39/385, 39/02, 39/09, 39/00  
US CL : 424/197.11, 234.1, 244.1, 184.1, 236.1, 831

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
U.S. : 424/197.11, 234.1, 244.1, 184.1, 236.1, 831

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
Please See Continuation Sheet

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/34771 A2 (CHIRON S.P.A.) 02 May 2002 (02.05.2002), pages 7, 841 and 842.	1-17
Y	US 6,372,222 B1 (MICHON et al) 16 April 2002 (16.04.2002), claims and Examples.	1-17
Y	US 6,426,074 B1 (MICHEL et al.) 30 July 2002 (30.06.2002), Example 14.	1-17

Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"E" earlier application or patent published on or after the international filing date

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"O" document referring to an oral disclosure, use, exhibition or other means

"&"

document member of the same patent family

"P" document published prior to the international filing date but later than the priority date claimed

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**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US03/29167

**Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claim Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claim Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3.  Claim Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:  
Please See Continuation Sheet

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

  

The additional search fees were accompanied by the applicant's protest.  
No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

PCT/US03/29167

**BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING**

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

GBS saccharide antigen species: serotype Ia; serotype Ib; and serotype III.

The claims are deemed to correspond to the species listed above in the following manner:  
Claims 1 and 17.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

The saccharide antigen species listed above do not share significant structural elements and immunogenicity specificity.

**Continuation of B. FIELDS SEARCHED Item 3:**

DIALOG, WEST, EMBASE, BIOSIS, MEDLINE

GBS or group B streptococcus?, (Ia or Ib or III), GBS79, GBS80 to GBS 691, inventor's name